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**WO 03/105770 A2**

(54) Title: CARBOCYCLIC NUCLEOSIDE DERIVATIVES AS INHIBITORS OF RNA-DEPENDENT RNA VIRAL POLYMERASE

(57) Abstract: The present invention provides carbocyclic nucleoside compounds and certain derivatives thereof which are inhibitors of RNA-dependent RNA viral polymerase. These compounds are inhibitors of RNA-dependent RNA viral replication and are useful for the treatment of RNA-dependent RNA viral infection. They are particularly useful as inhibitors of hepatitis C virus (HCV) NS5B polymerase, as inhibitors of HCV replication, and/or for the treatment of hepatitis C infection. The invention also describes pharmaceutical compositions containing such carbocyclic nucleoside compounds alone or in combination with other agents active against RNA-dependent RNA viral infection, in particular HCV infection. Also disclosed are methods of inhibiting RNA-dependent RNA polymerase, inhibiting RNA-dependent RNA viral replication, and/or treating RNA-dependent RNA viral infection with the carbocyclic nucleoside compounds of the present invention

## TITLE OF THE INVENTION

## CARBOCYCLIC NUCLEOSIDE DERIVATIVES AS INHIBITORS OF RNA-DEPENDENT RNA VIRAL POLYMERASE

## 5 FIELD OF THE INVENTION

The present invention is concerned with carbocyclic nucleoside compounds and certain derivatives thereof, their synthesis, and their use as inhibitors of RNA-dependent RNA viral polymerase. The compounds of the present invention are inhibitors of RNA-dependent RNA viral replication and are useful for the 10 treatment of RNA-dependent RNA viral infection. They are particularly useful as inhibitors of hepatitis C virus (HCV) NS5B polymerase, as inhibitors of HCV replication, and for the treatment of hepatitis C infection.

## BACKGROUND OF THE INVENTION

15 Hepatitis C virus (HCV) infection is a major health problem that leads to chronic liver disease, such as cirrhosis and hepatocellular carcinoma, in a substantial number of infected individuals, estimated to be 2-15% of the world's population. There are an estimated 4.5 million infected people in the United States alone, according to the U.S. Center for Disease Control. According to the World 20 Health Organization, there are more than 200 million infected individuals worldwide, with at least 3 to 4 million people being infected each year. Once infected, about 20% of people clear the virus, but the rest harbor HCV the rest of their lives. Ten to twenty percent of chronically infected individuals eventually develop liver-destroying cirrhosis or cancer. The viral disease is transmitted parenterally by contaminated 25 blood and blood products, contaminated needles, or sexually and vertically from infected mothers or carrier mothers to their off-spring. Current treatments for HCV infection, which are restricted to immunotherapy with recombinant interferon- $\alpha$  or pegylated interferon- $\alpha$ , alone or in combination with the nucleoside analog ribavirin, are effective in only about 50% of the infected population (J. Gillis, "Doctors Close in 30 on Hepatitis C Suppression, Data Show," Washington Post, Thursday, April 18, 2002). Moreover, there is no established vaccine for HCV. Consequently, there is a continuing need for improved therapeutic agents that effectively combat chronic HCV infection. The state of the art in the treatment of HCV infection has been reviewed, and reference is made to the following publications: B. Dymock, et al., "Novel 35 approaches to the treatment of hepatitis C virus infection," Antiviral Chemistry &

Chemotherapy, 11: 79-96 (2000); H. Rosen, et al., "Hepatitis C virus: current understanding and prospects for future therapies," Molecular Medicine Today, 5: 393-399 (1999); D. Moradpour, et al., "Current and evolving therapies for hepatitis C," European J. Gastroenterol. Hepatol., 11: 1189-1202 (1999); R. Bartenschlager,  
5 "Candidate Targets for Hepatitis C Virus-Specific Antiviral Therapy," Intervirology, 40: 378-393 (1997); G.M. Lauer and B.D. Walker, "Hepatitis C Virus Infection," N. Engl. J. Med., 345: 41-52 (2001); B.W. Dymock, "Emerging therapies for hepatitis C virus infection," Emerging Drugs, 6: 13-42 (2001); and C. Crabb, "Hard-Won Advances Spark Excitement about Hepatitis C," Science: 506-507 (2001); the  
10 contents of all of which are incorporated by reference herein in their entirety.

Different approaches to HCV therapy have been taken, which include the inhibition of viral serine proteinase (NS3 protease), helicase, and RNA-dependent RNA polymerase (NS5B), and the development of a vaccine.

The HCV virion is an enveloped positive-strand RNA virus with a  
15 single oligoribonucleotide genomic sequence of about 9600 bases which encodes a polyprotein of about 3,010 amino acids. The protein products of the HCV gene consist of the structural proteins C, E1, and E2, and the non-structural proteins NS2, NS3, NS4A and NS4B, and NS5A and NS5B. The nonstructural (NS) proteins are believed to provide the catalytic machinery for viral replication. The NS3 protease  
20 releases NS5B, the RNA-dependent RNA polymerase from the polyprotein chain. HCV NS5B polymerase is required for the synthesis of a double-stranded RNA from a single-stranded viral RNA that serves as a template in the replication cycle of HCV. NS5B polymerase is therefore considered to be an essential component in the HCV replication complex [see K. Ishii, et al., "Expression of Hepatitis C Virus NS5B  
25 Protein: Characterization of Its RNA Polymerase Activity and RNA Binding," Hepatology, 29: 1227-1235 (1999) and V. Lohmann, et al., "Biochemical and Kinetic Analyses of NS5B RNA-Dependent RNA Polymerase of the Hepatitis C Virus," Virology, 249: 108-118 (1998)]. Inhibition of HCV NS5B polymerase prevents formation of the double-stranded HCV RNA and therefore constitutes an attractive  
30 approach to the development of HCV-specific antiviral therapies.

It has now been found that carbocyclic nucleoside compounds of the present invention and certain derivatives thereof are potent inhibitors of RNA-dependent RNA viral replication and in particular HCV replication. The 5'-triphosphate derivatives of these carbocyclic nucleoside compounds are inhibitors of  
35 RNA-dependent RNA viral polymerase and in particular HCV NS5B polymerase.

The instant carbocyclic nucleoside compounds and derivatives thereof are useful to treat RNA-dependent RNA viral infection and in particular HCV infection.

It is therefore an object of the present invention to provide carbocyclic nucleoside compounds and certain derivatives thereof which are useful as inhibitors 5 of RNA-dependent RNA viral polymerase and in particular as inhibitors of HCV NS5B polymerase.

It is another object of the present invention to provide carbocyclic nucleoside compounds and certain derivatives thereof which are useful as inhibitors of the replication of an RNA-dependent RNA virus and in particular as inhibitors of 10 the replication of hepatitis C virus.

It is another object of the present invention to provide carbocyclic nucleoside compounds and certain derivatives thereof which are useful in the treatment of RNA-dependent RNA viral infection and in particular in the treatment of HCV infection.

15 It is another object of the present invention to provide pharmaceutical compositions comprising the carbocyclic nucleoside compounds of the present invention in association with a pharmaceutically acceptable carrier.

It is another object of the present invention to provide pharmaceutical 20 compositions comprising the carbocyclic nucleoside compounds and derivatives thereof of the present invention for use as inhibitors of RNA-dependent RNA viral polymerase and in particular as inhibitors of HCV NS5B polymerase.

It is another object of the present invention to provide pharmaceutical compositions comprising the carbocyclic nucleoside compounds and derivatives 25 thereof of the present invention for use as inhibitors of RNA-dependent RNA viral replication and in particular as inhibitors of HCV replication.

It is another object of the present invention to provide pharmaceutical compositions comprising the carbocyclic nucleoside compounds and derivatives thereof of the present invention for use in the treatment of RNA-dependent RNA viral infection and in particular in the treatment of HCV infection.

30 It is another object of the present invention to provide pharmaceutical compositions comprising the carbocyclic nucleoside compounds and derivatives thereof of the present invention in combination with other agents active against an RNA-dependent RNA virus and in particular against HCV.

It is another object of the present invention to provide methods for the inhibition of RNA-dependent RNA viral polymerase and in particular for the inhibition of HCV NS5B polymerase.

5 It is another object of the present invention to provide methods for the inhibition of RNA-dependent RNA viral replication and in particular for the inhibition of HCV replication.

It is another object of the present invention to provide methods for the treatment of RNA-dependent RNA viral infection and in particular for the treatment of HCV infection.

10 It is another object of the present invention to provide methods for the treatment of RNA-dependent RNA viral infection in combination with other agents active against RNA-dependent RNA virus and in particular for the treatment of HCV infection in combination with other agents active against HCV.

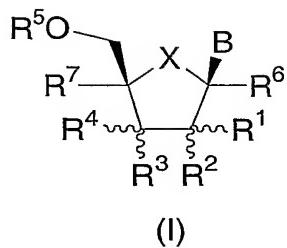
15 It is another object of the present invention to provide carbocyclic nucleoside compounds and certain derivatives thereof and their pharmaceutical compositions for use as a medicament for the inhibition of RNA-dependent RNA viral replication and/or the treatment of RNA-dependent RNA viral infection and in particular for the inhibition of HCV replication and/or the treatment of HCV infection.

20 It is another object of the present invention to provide for the use of the carbocyclic nucleoside compounds and certain derivatives thereof of the present invention and their pharmaceutical compositions for the manufacture of a medicament for the inhibition of RNA-dependent RNA viral replication and/or the treatment of RNA-dependent RNA viral infection and in particular for the inhibition of HCV replication and/or the treatment of HCV infection.

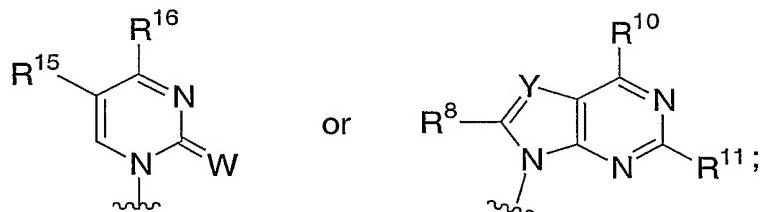
25 These and other objects will become readily apparent from the detailed description which follows.

#### SUMMARY OF THE INVENTION

30 The present invention relates to compounds of structural formula I of the indicated stereochemical configuration:



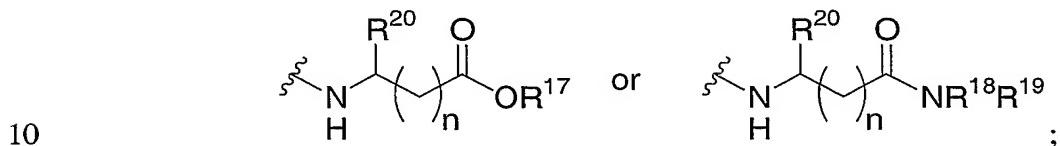
or a pharmaceutically acceptable salt thereof; wherein  
B is



- 5    X is CH<sub>2</sub>, CHF, CF<sub>2</sub>, or C=CH<sub>2</sub>;
- Y is N or C-R<sup>9</sup>;
- W is O or S;
- R<sup>1</sup> is C<sub>2</sub>-4 alkenyl, C<sub>2</sub>-4 alkynyl, or C<sub>1</sub>-4 alkyl, wherein alkyl is unsubstituted or substituted with hydroxy, amino, C<sub>1</sub>-4 alkoxy, C<sub>1</sub>-4 alkylthio, or one to three fluorine atoms;
- 10    R<sup>2</sup> is hydrogen, fluorine, amino, hydroxy, mercapto, C<sub>1</sub>-4 alkoxy, C<sub>1</sub>-8 alkylcarbonyloxy, or C<sub>1</sub>-4 alkyl;
- R<sup>3</sup> and R<sup>4</sup> are each independently selected from the group consisting of hydrogen, cyano, azido, halogen, hydroxy, mercapto, amino, C<sub>1</sub>-4 alkoxy, C<sub>1</sub>-8 alkylcarbonyloxy, C<sub>2</sub>-4 alkenyl, C<sub>2</sub>-4 alkynyl, and C<sub>1</sub>-4 alkyl, wherein alkyl is unsubstituted or substituted with hydroxy, amino, C<sub>1</sub>-4 alkoxy, C<sub>1</sub>-4 alkylthio, or one to three fluorine atoms;
- 15    R<sup>5</sup> is hydrogen, C<sub>1</sub>-10 alkylcarbonyl, P<sub>3</sub>O<sub>9</sub>H<sub>4</sub>, P<sub>2</sub>O<sub>6</sub>H<sub>3</sub>, or P(O)R<sup>13</sup>R<sup>14</sup>;
- R<sup>6</sup> and R<sup>7</sup> are each independently hydrogen, methyl, hydroxymethyl, or fluoromethyl;
- 20    R<sup>8</sup> is hydrogen, C<sub>1</sub>-4 alkyl, C<sub>2</sub>-4 alkynyl, halogen, cyano, carboxy, C<sub>1</sub>-4 alkyloxycarbonyl, azido, amino, C<sub>1</sub>-4 alkylamino, di(C<sub>1</sub>-4 alkyl)amino, hydroxy, C<sub>1</sub>-6 alkoxy, C<sub>1</sub>-6 alkylthio, C<sub>1</sub>-6 alkylsulfonyl, or (C<sub>1</sub>-4 alkyl)0-2 aminomethyl;
- R<sup>9</sup> is hydrogen, halogen, cyano, nitro, NHCONH<sub>2</sub>, CONR<sup>12</sup>R<sup>12</sup>, CSNR<sup>12</sup>R<sup>12</sup>, COOR<sup>12</sup>, C(=NH)NH<sub>2</sub>, hydroxy, C<sub>1</sub>-3 alkoxy, amino, C<sub>1</sub>-4 alkylamino, di(C<sub>1</sub>-4

alkyl)amino, or C<sub>1-3</sub> alkyl, wherein alkyl is unsubstituted or substituted with one to three groups independently selected from halogen, amino, hydroxy, carboxy, and C<sub>1-3</sub> alkoxy;

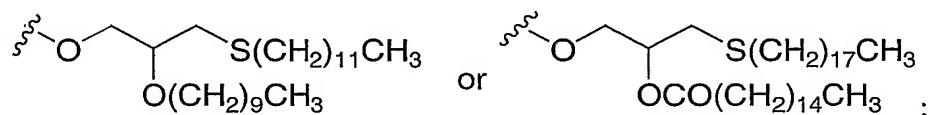
- 5 R<sub>10</sub> and R<sub>16</sub> are each independently hydrogen, hydroxy, mercapto, halogen, C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> alkylthio, C<sub>1-8</sub> alkylcarbonyloxy, C<sub>3-6</sub> cycloalkylcarbonyloxy, C<sub>1-8</sub> alkyloxycarbonyloxy, C<sub>3-6</sub> cycloalkyloxycarbonyloxy, -OCH<sub>2</sub>CH<sub>2</sub>SC(=O)C<sub>1-4</sub> alkyl, -OCH<sub>2</sub>O(C=O)C<sub>1-4</sub> alkyl, -OCH(C<sub>1-4</sub> alkyl)O(C=O)C<sub>1-4</sub> alkyl, amino, C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub> alkyl)amino, C<sub>3-6</sub> cycloalkylamino, di(C<sub>3-6</sub> cycloalkyl)amino, or an amino acyl residue having structural formula



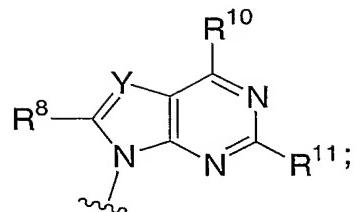
n is 0, 1, or 2;

R<sub>11</sub> is hydrogen, hydroxy, halogen, C<sub>1-4</sub> alkoxy, amino, C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub> alkyl)amino, C<sub>3-6</sub> cycloalkylamino, or di(C<sub>3-6</sub> cycloalkylamino); each R<sub>12</sub> is independently hydrogen or C<sub>1-6</sub> alkyl;

- 15 R<sub>17</sub>, R<sub>18</sub>, and R<sub>19</sub> are each independently hydrogen or C<sub>1-6</sub> alkyl;  
R<sub>13</sub> and R<sub>14</sub> are each independently hydroxy, -OCH<sub>2</sub>CH<sub>2</sub>SC(=O)C<sub>1-4</sub> alkyl, -OCH<sub>2</sub>O(C=O)OC<sub>1-4</sub> alkyl, -NHCHMeCO<sub>2</sub>Me, -OCH(C<sub>1-4</sub> alkyl)O(C=O)C<sub>1-4</sub> alkyl,



- 20 R<sub>15</sub> is hydrogen, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-4</sub> alkylamino, CF<sub>3</sub>, or halogen; and  
R<sub>20</sub> is hydrogen, C<sub>1-4</sub> alkyl, or phenyl C<sub>0-2</sub> alkyl;  
with the proviso that when B is



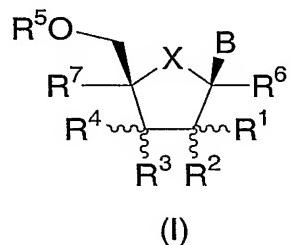
X is CH<sub>2</sub>; Y is N; R<sup>10</sup> is NH<sub>2</sub>; R<sup>2</sup> and R<sup>3</sup> are α-OH; and R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, and R<sup>11</sup> are hydrogen, then R<sup>1</sup> is not β-methyl.

- The compounds of formula I are useful as inhibitors of RNA-dependent RNA viral polymerase and in particular of HCV NS5B polymerase. They are also inhibitors of RNA-dependent RNA viral replication and in particular of HCV replication and are useful for the treatment of RNA-dependent RNA viral infection and in particular for the treatment of HCV infection.

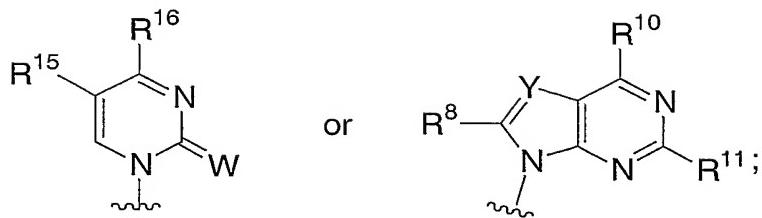
- Also encompassed within the present invention are pharmaceutical compositions containing the compounds alone or in combination with other agents active against RNA-dependent RNA virus and in particular against HCV as well as methods for the inhibition of RNA-dependent RNA viral replication and for the treatment of RNA-dependent RNA viral infection.

## 15 DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to compounds of structural formula I of the indicated stereochemical configuration:



- or a pharmaceutically acceptable salt thereof; wherein  
20 n is 0, 1, or 2;  
B is

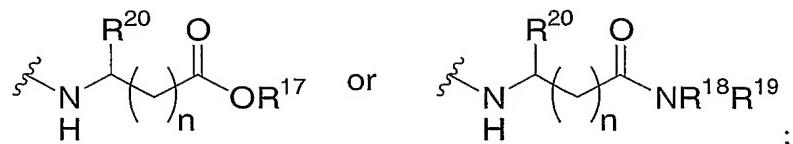


X is CH<sub>2</sub>, CHF, CF<sub>2</sub>, or C=CH<sub>2</sub>;

Y is N or C-R<sup>9</sup>;

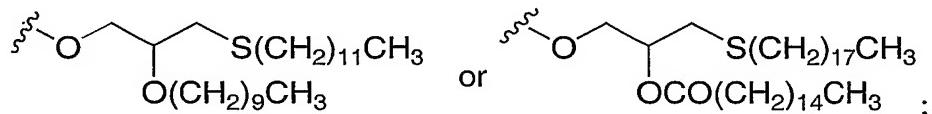
W is O or S;

- 5 R<sup>1</sup> is C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, or C<sub>1-4</sub> alkyl, wherein alkyl is unsubstituted or substituted with hydroxy, amino, C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> alkylthio, or one to three fluorine atoms;
- R<sup>2</sup> is hydrogen, fluorine, amino, hydroxy, mercapto, C<sub>1-4</sub> alkoxy, C<sub>1-8</sub> alkylcarbonyloxy, or C<sub>1-4</sub> alkyl;
- 10 R<sup>3</sup> and R<sup>4</sup> are each independently selected from the group consisting of hydrogen, cyano, azido, halogen, hydroxy, mercapto, amino, C<sub>1-4</sub> alkoxy, C<sub>1-8</sub> alkylcarbonyloxy, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, and C<sub>1-4</sub> alkyl, wherein alkyl is unsubstituted or substituted with hydroxy, amino, C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> alkylthio, or one to three fluorine atoms;
- 15 R<sup>5</sup> is hydrogen, C<sub>1-10</sub> alkylcarbonyl, P<sub>3</sub>O<sub>9</sub>H<sub>4</sub>, P<sub>2</sub>O<sub>6</sub>H<sub>3</sub>, or P(O)R<sup>13</sup>R<sup>14</sup>;
- R<sup>6</sup> and R<sup>7</sup> are each independently hydrogen, methyl, hydroxymethyl, or fluoromethyl;
- R<sup>8</sup> is hydrogen, C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkynyl, halogen, cyano, carboxy, C<sub>1-4</sub> alkyloxycarbonyl, azido, amino, C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub> alkyl)amino, hydroxy, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfonyl, or (C<sub>1-4</sub> alkyl)<sub>0-2</sub> aminomethyl;
- 20 R<sup>9</sup> is hydrogen, halogen, cyano, nitro, NHCONH<sub>2</sub>, CONR<sup>12</sup>R<sup>12</sup>, CSNR<sup>12</sup>R<sup>12</sup>, COOR<sup>12</sup>, C(=NH)NH<sub>2</sub>, hydroxy, C<sub>1-3</sub> alkoxy, amino, C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub> alkyl)amino, or C<sub>1-3</sub> alkyl, wherein alkyl is unsubstituted or substituted with one to three groups independently selected from halogen, amino, hydroxy, carboxy, and C<sub>1-3</sub> alkoxy;
- 25 R<sup>10</sup> and R<sup>16</sup> are each independently hydrogen, hydroxy, mercapto, halogen, C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> alkylthio, C<sub>1-8</sub> alkylcarbonyloxy, C<sub>3-6</sub> cycloalkylcarbonyloxy, C<sub>1-8</sub> alkyloxycarbonyloxy, C<sub>3-6</sub> cycloalkyloxycarbonyloxy, -OCH<sub>2</sub>CH<sub>2</sub>SC(=O)C<sub>1-4</sub> alkyl, -OCH<sub>2</sub>O(C=O)C<sub>1-4</sub> alkyl, -OCH(C<sub>1-4</sub> alkyl)O(C=O)C<sub>1-4</sub> alkyl, amino, C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub> alkyl)amino, C<sub>3-6</sub> cycloalkylamino, di(C<sub>3-6</sub> cycloalkyl)amino,
- 30 or an amino acyl residue having structural formula

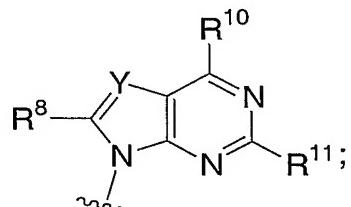


R11 is hydrogen, hydroxy, halogen, C1-4 alkoxy, amino, C1-4 alkylamino, di(C1-4 alkyl)amino, C3-6 cycloalkylamino, or di(C3-6 cycloalkylamino); each R12 is independently hydrogen or C1-6 alkyl;

- 5 R17, R18, and R19 are each independently hydrogen or C1-6 alkyl; R13 and R14 are each independently hydroxy, -OCH<sub>2</sub>CH<sub>2</sub>SC(=O)C1-4 alkyl, -OCH<sub>2</sub>O(C=O)OC1-4 alkyl, -NHCHMeCO<sub>2</sub>Me, -OCH(C1-4 alkyl)O(C=O)C1-4 alkyl,



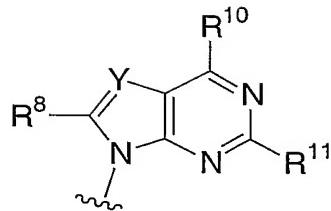
- 10 R15 is hydrogen, C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C1-4 alkylamino, CF<sub>3</sub>, or halogen; and R20 is hydrogen, C1-4 alkyl, or phenyl C0-2 alkyl; with the proviso that when B is



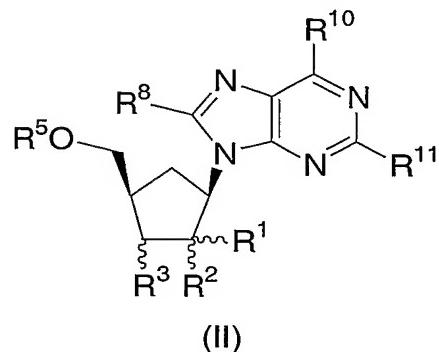
- 15 X is CH<sub>2</sub>; Y is N; R<sup>10</sup> is NH<sub>2</sub>; R<sup>2</sup> and R<sup>3</sup> are α-OH; and R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, and R<sup>11</sup> are hydrogen, then R<sup>1</sup> is not β-methyl.

The compounds of formula I are useful as inhibitors of RNA-dependent RNA viral polymerase. They are also inhibitors of RNA-dependent RNA viral replication and are useful for the treatment of RNA-dependent RNA viral infection.

In one embodiment of the compounds of structural formula I, B is



In a class of this embodiment are compounds of structural formula II:

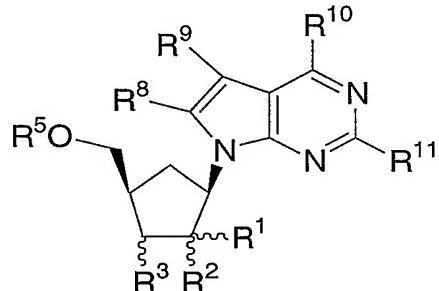


wherein

- 5    R<sup>1</sup> is C<sub>1</sub>-3 alkyl, wherein alkyl is unsubstituted or substituted with one to three fluorine atoms;
- R<sup>2</sup> is hydroxy, fluoro, C<sub>1</sub>-3 alkoxy, or C<sub>1</sub>-8 alkylcarbonyloxy;
- R<sup>3</sup> is hydrogen, halogen, hydroxy, amino, C<sub>1</sub>-3 alkoxy, or C<sub>1</sub>-8 alkylcarbonyloxy;
- R<sup>5</sup> is hydrogen, C<sub>1</sub>-8 alkylcarbonyl, P<sub>3</sub>O<sub>9</sub>H<sub>4</sub>, P<sub>2</sub>O<sub>6</sub>H<sub>3</sub>, or PO<sub>3</sub>H<sub>2</sub>;
- 10    R<sup>8</sup> is hydrogen, amino, or C<sub>1</sub>-4 alkylamino; and
- R<sup>10</sup> and R<sup>11</sup> are each independently hydrogen, halogen, hydroxy, amino, C<sub>1</sub>-4 alkylamino, di(C<sub>1</sub>-4 alkyl)amino, or C<sub>3</sub>-6 cycloalkylamino;
- with the proviso that when R<sup>10</sup> is NH<sub>2</sub>, R<sup>2</sup> and R<sup>3</sup> are α-OH, and R<sup>5</sup>, R<sup>8</sup>, and R<sup>11</sup> are hydrogen, then R<sup>1</sup> is not β-methyl.
- 15    In a subclass of this class,
- R<sup>1</sup> is methyl, fluoromethyl, difluoromethyl, or trifluoromethyl;
- R<sup>2</sup> is hydroxy, fluoro, or methoxy;
- R<sup>3</sup> is hydrogen, fluoro, hydroxy, amino, or methoxy;
- R<sup>5</sup> is hydrogen or P<sub>3</sub>O<sub>9</sub>H<sub>4</sub>;
- 20    R<sup>8</sup> is hydrogen or amino; and
- R<sup>10</sup> and R<sup>11</sup> are each independently hydrogen, fluoro, hydroxy, or amino;

with the proviso that when R<sup>10</sup> is NH<sub>2</sub>, R<sup>2</sup> and R<sup>3</sup> are  $\alpha$ -OH, and R<sup>5</sup>, R<sup>8</sup>, and R<sup>11</sup> are hydrogen, then R<sup>1</sup> is not  $\beta$ -methyl.

In another class of this embodiment are compounds of structural formula III:



(III)

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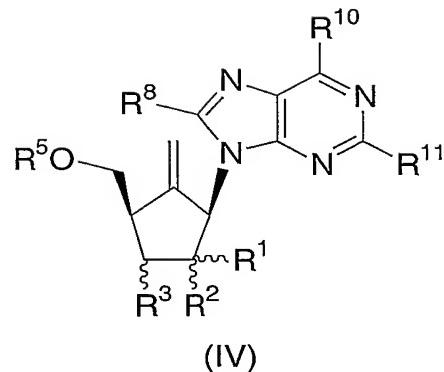
wherein

- R<sup>1</sup> is C<sub>1-3</sub> alkyl, wherein alkyl is unsubstituted or substituted with one to three fluorine atoms;
- R<sup>2</sup> is hydroxy, fluoro, C<sub>1-3</sub> alkoxy, or C<sub>1-8</sub> alkylcarbonyloxy;
- 10 R<sup>3</sup> is hydrogen, halogen, hydroxy, amino, C<sub>1-3</sub> alkoxy, or C<sub>1-8</sub> alkylcarbonyloxy;
- R<sup>5</sup> is hydrogen, C<sub>1-8</sub> alkylcarbonyl, P<sub>3</sub>O<sub>9</sub>H<sub>4</sub>, P<sub>2</sub>O<sub>6</sub>H<sub>3</sub>, or PO<sub>3</sub>H<sub>2</sub>;
- R<sup>8</sup> is hydrogen, amino, or C<sub>1-4</sub> alkylamino;
- R<sup>9</sup> is hydrogen, cyano, methyl, halogen, CONH<sub>2</sub> or CSNH<sub>2</sub>; and
- R<sup>10</sup> and R<sup>11</sup> are each independently hydrogen, halogen, hydroxy, amino, C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub> alkyl)amino, or C<sub>3-6</sub> cycloalkylamino.

In a subclass of this class,

- R<sup>1</sup> is methyl, fluoromethyl, difluoromethyl, or trifluoromethyl;
- R<sup>2</sup> is hydroxy, fluoro, or methoxy;
- 20 R<sup>3</sup> is hydrogen, fluoro, hydroxy, amino, or methoxy;
- R<sup>5</sup> is hydrogen or P<sub>3</sub>O<sub>9</sub>H<sub>4</sub>;
- R<sup>8</sup> is hydrogen or amino;
- R<sup>9</sup> is hydrogen, cyano, methyl, halogen, CONH<sub>2</sub> or CSNH<sub>2</sub>; and
- R<sup>10</sup> and R<sup>11</sup> are each independently hydrogen, fluoro, hydroxy, or amino.

In a third class of this embodiment are compounds of structural formula IV:



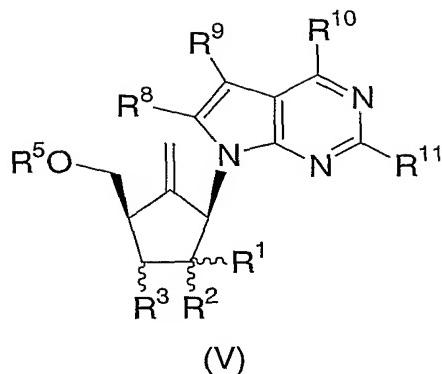
wherein

- $R^1$  is C<sub>1-3</sub> alkyl, wherein alkyl is unsubstituted or substituted with one to three fluorine atoms;
- 5     $R^2$  is hydroxy, fluoro, C<sub>1-3</sub> alkoxy, or C<sub>1-8</sub> alkylcarbonyloxy;
- $R^3$  is hydrogen, halogen, hydroxy, amino, C<sub>1-3</sub> alkoxy, or C<sub>1-8</sub> alkylcarbonyloxy;
- $R^5$  is hydrogen, C<sub>1-8</sub> alkylcarbonyl, P<sub>3</sub>O<sub>9</sub>H<sub>4</sub>, P<sub>2</sub>O<sub>6</sub>H<sub>3</sub>, or PO<sub>3</sub>H<sub>2</sub>;
- $R^8$  is hydrogen, amino, or C<sub>1-4</sub> alkylamino; and
- $R^{10}$  and  $R^{11}$  are each independently hydrogen, halogen, hydroxy, amino,
- 10    C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub> alkyl)amino, or C<sub>3-6</sub> cycloalkylamino.

In a subclass of this class,

- $R^1$  is methyl, fluoromethyl, difluoromethyl, or trifluoromethyl;
- $R^2$  is hydroxy, fluoro, or methoxy;
- $R^3$  is hydrogen, fluoro, hydroxy, amino, or methoxy;
- 15     $R^5$  is hydrogen or P<sub>3</sub>O<sub>9</sub>H<sub>4</sub>;
- $R^8$  is hydrogen or amino; and
- $R^{10}$  and  $R^{11}$  are each independently hydrogen, fluoro, hydroxy, or amino.

In a fourth class of this embodiment are compounds of structural formula V:



wherein

- R<sup>1</sup> is C<sub>1-3</sub> alkyl, wherein alkyl is unsubstituted or substituted with one to three fluorine atoms;
- 5 R<sup>2</sup> is hydroxy, fluoro, C<sub>1-3</sub> alkoxy, or C<sub>1-8</sub> alkylcarbonyloxy;
- R<sup>3</sup> is hydrogen, halogen, hydroxy, amino, C<sub>1-3</sub> alkoxy, or C<sub>1-8</sub> alkylcarbonyloxy;
- R<sup>5</sup> is hydrogen, C<sub>1-8</sub> alkylcarbonyl, P<sub>3</sub>O<sub>9</sub>H<sub>4</sub>, P<sub>2</sub>O<sub>6</sub>H<sub>3</sub>, or PO<sub>3</sub>H<sub>2</sub>;
- R<sup>8</sup> is hydrogen, amino, or C<sub>1-4</sub> alkylamino;
- R<sup>9</sup> is hydrogen, cyano, methyl, halogen, CONH<sub>2</sub> or CSNH<sub>2</sub>; and
- 10 R<sup>10</sup> and R<sup>11</sup> are each independently hydrogen, halogen, hydroxy, amino, C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub> alkyl)amino, or C<sub>3-6</sub> cycloalkylamino.

In a subclass of this class,

- R<sup>1</sup> is methyl, fluoromethyl, difluoromethyl, or trifluoromethyl;
- R<sup>2</sup> is hydroxy, fluoro, or methoxy;
- 15 R<sup>3</sup> is hydrogen, fluoro, hydroxy, amino, or methoxy;
- R<sup>5</sup> is hydrogen or P<sub>3</sub>O<sub>9</sub>H<sub>4</sub>;
- R<sup>8</sup> is hydrogen or amino;
- R<sup>9</sup> is hydrogen, cyano, methyl, halogen, CONH<sub>2</sub> or CSNH<sub>2</sub>;
- R<sup>10</sup> and R<sup>11</sup> are each independently hydrogen, fluoro, hydroxy, or amino.

20

Illustrative, but nonlimiting, examples of compounds of the present invention of structural formula I which are useful as inhibitors of RNA-dependent RNA viral polymerase are the following:

- 25 2-amino-7-[(1 $\beta$ ,2 $\alpha$ OH,3 $\alpha$ ,4 $\beta$ )-2,3-dihydroxy-4-hydroxymethyl-2-methyl-5-methylenecyclopentyl]-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;

2-amino-7-[(1R,2S,3R,4R)-2,3-dihydroxy-4-hydroxymethyl-2-methyl-5-methylenecyclopentyl]-3,7-dihydro-4*H*-pyrrolo[2,3-d]pyrimidin-4-one;

5 (1 $\alpha$ OH,2 $\alpha$ ,3 $\beta$ ,5 $\beta$ )-5-(4-amino-7*H*-pyrrolo[2,3-d]pyrimidin-7-yl)-3-hydroxymethyl-1-methyl-4- methylenecyclopentane-1,2-diol;

(1S,2R,3R,5R)-5-(4-amino-7*H*-pyrrolo[2,3-d]pyrimidin-7-yl)-3-hydroxymethyl-1-methyl-4- methylenecyclopentane-1,2-diol;

10 (1 $\beta$ ,2 $\alpha$ OH,3 $\alpha$ ,4 $\beta$ )-2-amino-9-[2,3-dihydroxy-4-(hydroxymethyl)-2-methyl-5-methylenecyclopentyl]-1,9-dihydro-6*H*-purin-6-one;

15 2-amino-9-[(1R,2S,3R,4R)-2,3-dihydroxy-4-(hydroxymethyl)-2-methyl-5-methylenecyclopentyl]-1,9-dihydro-6*H*-purin-6-one;

(1S,2R,3R,5R)-5-(6-amino-9*H*-purin-9-yl)-3-(hydroxymethyl)-1-methyl-4-methylenecyclopentane-1,2-diol;

20 (1 $\alpha$ OH,2 $\alpha$ ,3 $\beta$ ,5 $\beta$ )-5-(6-amino-9*H*-purin-9-yl)-3-(hydroxymethyl)-1-methyl-4-methylenecyclopentane-1,2-diol;

(1RS,2R,3R,5R)-5-(4-amino-7*H*-pyrrolo[2,3-d]pyrimidin-7-yl)-3-(hydroxymethyl)-1-methylcyclopentanediol-1,2-diol;

25 (1S,2R,3R,5R)-5-(4-amino-7*H*-pyrrolo[2,3-d]pyrimidin-7-yl)-3-(hydroxymethyl)-1-methylcyclopentanediol-1,2-diol;

(1RS,2R,3R,5R)-5-(6-amino-9*H*-purin-9-yl)-3-(hydroxymethyl)-1-methylcyclopentanediol-1,2-diol;

(1S,2R,3R,5R)-5-(6-amino-9*H*-purin-9-yl)-3-(hydroxymethyl)-1-methylcyclopentanediol-1,2-diol;

2-amino-9-[(1R,2RS,3R,4R)-2,3-dihydroxy-4-(hydroxymethyl)-2-methylcyclopentyl]-1,9-dihydro-6*H*-purin-6-one;

5        2-amino-9-[(1R,2S,3R,4R)-2,3-dihydroxy-4-(hydroxymethyl)-2-methylcyclopentyl]-1,9-dihydro-6*H*-purin-6-one;

2-amino-7-[(1R,2RS,3R,4R)-2,3-dihydroxy-4-(hydroxymethyl)-2-methylcyclopentyl]-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one; and

10      2-amino-7-[(1R,2S,3R,4R)-2,3-dihydroxy-4-(hydroxymethyl)-2-methylcyclopentyl]-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;

and the corresponding 5'-triphosphates;

or a pharmaceutically acceptable salt thereof.

15            In one embodiment of the present invention, the carbocyclic nucleoside compounds of the present invention are useful as inhibitors of positive-sense single-stranded RNA-dependent RNA viral polymerase, inhibitors of positive-sense single-stranded RNA-dependent RNA viral replication, and/or for the treatment of positive-sense single-stranded RNA-dependent RNA viral infection. In a class of this embodiment, the positive-sense single-stranded RNA-dependent RNA virus is a *Flaviviridae* virus or a *Picornaviridae* virus. In a subclass of this class, the *Picornaviridae* virus is a rhinovirus, a poliovirus, or a hepatitis A virus. In a second subclass of this class, the *Flaviviridae* virus is selected from the group consisting of hepatitis C virus, yellow fever virus, dengue virus, West Nile virus, Japanese encephalitis virus, Banzi virus, and bovine viral diarrhea virus (BVDV). In a subclass of this subclass, the *Flaviviridae* virus is hepatitis C virus.

Another aspect of the present invention is concerned with a method for inhibiting RNA-dependent RNA viral polymerase, a method for inhibiting RNA-dependent RNA viral replication, and/or a method for treating RNA-dependent RNA viral infection in a mammal in need thereof comprising administering to the mammal a therapeutically effective amount of a compound of structural formula I.

30            In one embodiment of this aspect of the present invention, the RNA-dependent RNA viral polymerase is a positive-sense single-stranded RNA-dependent RNA viral polymerase. In a class of this embodiment, the positive-sense single-stranded RNA-dependent RNA viral polymerase is a *Flaviviridae* viral polymerase or

a *Picornaviridae* viral polymerase. In a subclass of this class, the *Picornaviridae* viral polymerase is rhinovirus polymerase, poliovirus polymerase, or hepatitis A virus polymerase. In a second subclass of this class, the *Flaviviridae* viral polymerase is selected from the group consisting of hepatitis C virus polymerase, yellow fever virus 5 polymerase, dengue virus polymerase, West Nile virus polymerase, Japanese encephalitis virus polymerase, Banzi virus polymerase, and bovine viral diarrhea virus (BVDV) polymerase. In a subclass of this subclass, the *Flaviviridae* viral polymerase is hepatitis C virus polymerase.

In a second embodiment of this aspect of the present invention, the 10 RNA-dependent RNA viral replication is a positive-sense single-stranded RNA-dependent RNA viral replication. In a class of this embodiment, the positive-sense single-stranded RNA-dependent RNA viral replication is *Flaviviridae* viral replication or *Picornaviridae* viral replication. In a subclass of this class, the *Picornaviridae* viral replication is rhinovirus replication, poliovirus replication, or hepatitis A virus 15 replication. In a second subclass of this class, the *Flaviviridae* viral replication is selected from the group consisting of hepatitis C virus replication, yellow fever virus replication, dengue virus replication, West Nile virus replication, Japanese encephalitis virus replication, Banzi virus replication, and bovine viral diarrhea virus replication. In a subclass of this subclass, the *Flaviviridae* viral replication is hepatitis 20 C virus replication.

In a third embodiment of this aspect of the present invention, the RNA-dependent RNA viral infection is a positive-sense single-stranded RNA-dependent viral infection. In a class of this embodiment, the positive-sense single-stranded RNA-dependent RNA viral infection is *Flaviviridae* viral infection or *Picornaviridae* 25 viral infection. In a subclass of this class, the *Picornaviridae* viral infection is rhinovirus infection, poliovirus infection, or hepatitis A virus infection. In a second subclass of this class, the *Flaviviridae* viral infection is selected from the group consisting of hepatitis C virus infection, yellow fever virus infection, dengue virus infection, West Nile virus infection, Japanese encephalitis virus infection, Banzi virus 30 infection, and bovine viral diarrhea virus infection. In a subclass of this subclass, the *Flaviviridae* viral infection is hepatitis C virus infection.

Throughout the instant application, the following terms have the indicated meanings:

The alkyl groups specified above are intended to include those alkyl 35 groups of the designated length in either a straight or branched configuration.

Exemplary of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tertiary butyl, pentyl, isopentyl, hexyl, isoheptyl, and the like.

The term "alkenyl" shall mean straight or branched chain alkenes of two to six total carbon atoms, or any number within this range (e.g., ethenyl, propenyl, 5 butenyl, pentenyl, etc.).

The term "alkynyl" shall mean straight or branched chain alkynes of two to six total carbon atoms, or any number within this range (e.g., ethynyl, propynyl, butynyl, pentynyl, etc.).

The term "cycloalkyl" shall mean cyclic rings of alkanes of three to 10 eight total carbon atoms, or any number within this range (i.e., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl).

The term "cycloheteroalkyl" is intended to include non-aromatic 15 heterocycles containing one or two heteroatoms selected from nitrogen, oxygen and sulfur. Examples of 4-6-membered cycloheteroalkyl include azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, thiamorpholinyl, imidazolidinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiophenyl, piperazinyl, and the like.

The term "alkoxy" refers to straight or branched chain alkoxides of the number of carbon atoms specified (e.g., C<sub>1-4</sub> alkoxy), or any number within this range [i.e., methoxy (MeO-), ethoxy, isopropoxy, etc.].

The term "alkylthio" refers to straight or branched chain alkylsulfides of the number of carbon atoms specified (e.g., C<sub>1-4</sub> alkylthio), or any number within 20 this range [i.e., methylthio (MeS-), ethylthio, isopropylthio, etc.].

The term "alkylamino" refers to straight or branched alkylamines of the number of carbon atoms specified (e.g., C<sub>1-4</sub> alkylamino), or any number within 25 this range [i.e., methylamino, ethylamino, isopropylamino, t-butylamino, etc.].

The term "cycloalkylamino" refers to saturated aminohydrocarbons containing one ring of the number of carbon atoms specified (e.g., C<sub>3-6</sub> cycloalkylamino), or any number within this range [i.e., cyclopropylamino, cyclobutylamino, cyclopentylamino, and cyclohexylamino].

The term "alkylsulfonyl" refers to straight or branched chain 30 alkylsulfones of the number of carbon atoms specified (e.g., C<sub>1-6</sub> alkylsulfonyl), or any number within this range [i.e., methylsulfonyl (MeSO<sub>2</sub>-), ethylsulfonyl, isopropylsulfonyl, etc.].

The term "alkyloxycarbonyl" refers to straight or branched chain esters 35 of a carboxylic acid derivative of the present invention of the number of carbon atoms

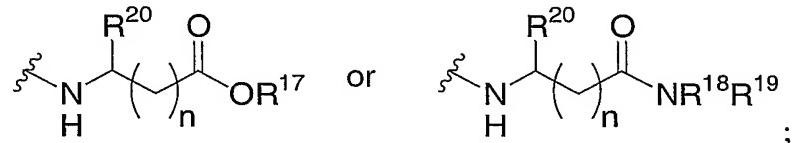
specified (e.g., C<sub>1</sub>-4 alkyloxycarbonyl), or any number within this range [i.e., methyloxycarbonyl (MeOCO-), ethyloxycarbonyl, or butyloxycarbonyl].

The term "aryl" includes both phenyl, naphthyl, and pyridyl. The phenyl, naphthyl, or pyridyl group wherever it occurs in the compounds of the present invention is optionally substituted with one to three groups independently selected from C<sub>1</sub>-4 alkyl, halogen, cyano, nitro, trifluoromethyl, C<sub>1</sub>-4 alkoxy, and C<sub>1</sub>-4 alkylthio.

The term "halogen" is intended to include the halogen atoms fluorine, chlorine, bromine and iodine.

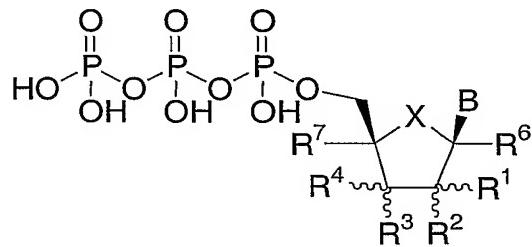
The term "substituted" shall be deemed to include multiple degrees of substitution by a named substituent. Where multiple substituent moieties are disclosed or claimed, the substituted compound can be independently substituted by one or more of the disclosed or claimed substituent moieties, singly or plurally.

The term "amino acyl residue" refers to an α-, β-, or γ-amino acyl group of structural formula

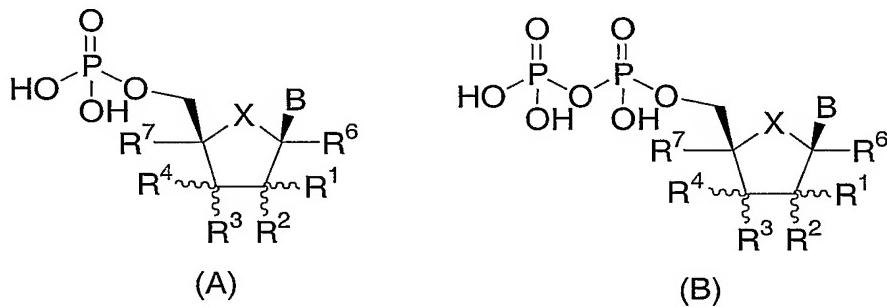


wherein n is 0, 1, or 2 and R<sub>17</sub>, R<sub>18</sub>, R<sub>19</sub>, and R<sub>20</sub> are as defined hereinabove. When R<sub>20</sub> is not hydrogen, the amino acyl residue contains an asymmetric center and is intended to include the individual R- and S-enantiomers as well as RS-racemic mixtures.

The term "5'-triphosphate" refers to a triphosphoric acid ester derivative of the 5'-hydroxyl group of a carbocyclic nucleoside compound of the present invention having the following general structural formula:



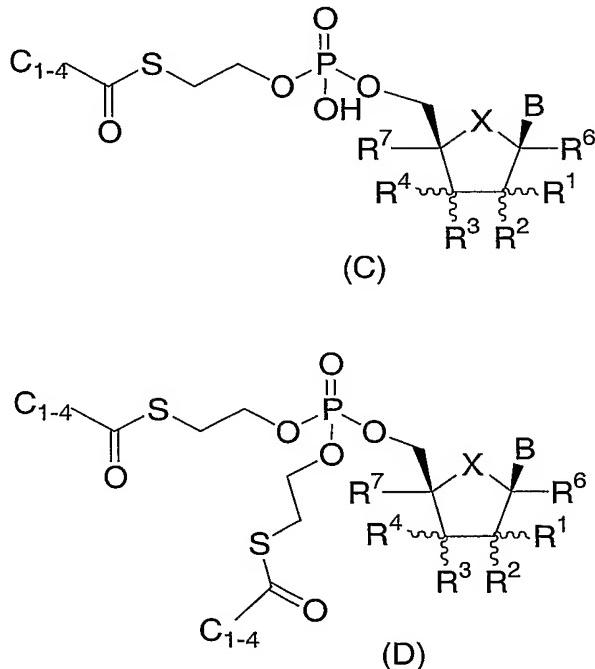
wherein B and R<sup>1</sup>-R<sup>11</sup> are as defined above. The compounds of the present invention are also intended to include pharmaceutically acceptable salts of the triphosphate ester as well as pharmaceutically acceptable salts of 5'-monophosphate and 5'-diphosphate ester derivatives of the structural formulae A and B, respectively,



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The term "5'-(S-acyl-2-thioethyl)phosphate" or "SATE" refers to a mono- or di-ester derivative of a 5'-monophosphate carbocyclic nucleoside derivative of the present invention of structural formulae C and D, respectively, as well as pharmaceutically acceptable salts of the mono-ester,

10



The term "composition," as in "pharmaceutical composition," is intended to encompass a product comprising the active ingredient(s) and the inert

ingredient(s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the  
5 pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier.

The terms "administration of" and "administering a" compound should be understood to mean providing a compound of the invention or a prodrug of a  
10 compound of the invention to the individual in need.

Another aspect of the present invention is concerned with a method of inhibiting HCV NS5B polymerase, inhibiting HCV replication, or treating HCV infection with a compound of the present invention in combination with one or more agents useful for treating HCV infection. Such agents active against HCV include,  
15 but are not limited to, ribavirin, levovirin, viramidine, thymosin alpha-1, interferon- $\beta$ , interferon- $\alpha$ , pegylated interferon- $\alpha$  (peginterferon- $\alpha$ ), a combination of interferon- $\alpha$  and ribavirin, a combination of peginterferon- $\alpha$  and ribavirin, a combination of interferon- $\alpha$  and levovirin, and a combination of peginterferon- $\alpha$  and levovirin. Interferon- $\alpha$  includes, but is not limited to, recombinant interferon- $\alpha$ 2a (such as  
20 Roferon interferon available from Hoffmann-LaRoche, Nutley, NJ), pegylated interferon- $\alpha$ 2a (Pegasys<sup>TM</sup>), interferon- $\alpha$ 2b (such as Intron-A interferon available from Schering Corp., Kenilworth, NJ), pegylated interferon- $\alpha$ 2b (PegIntron<sup>TM</sup>), a recombinant consensus interferon (such as interferon alphacon-1), and a purified interferon- $\alpha$  product. Amgen's recombinant consensus interferon has the brand name  
25 Infergen®. Levovirin is the L-enantiomer of ribavirin which has shown immunomodulatory activity similar to ribavirin. Viramidine represents an analog of ribavirin disclosed in WO 01/60379 (assigned to ICN Pharmaceuticals). In accordance with this method of the present invention, the individual components of the combination can be administered separately at different times during the course of  
30 therapy or concurrently in divided or single combination forms. The instant invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment, and the term "administering" is to be interpreted accordingly. It will be understood that the scope of combinations of the compounds of this invention with other agents useful for treating HCV infection includes in principle any  
35 combination with any pharmaceutical composition for treating HCV infection. When

a compound of the present invention or a pharmaceutically acceptable salt thereof is used in combination with a second therapeutic agent active against HCV, the dose of each compound may be either the same as or different from the dose when the compound is used alone.

5 For the treatment of HCV infection, the compounds of the present invention may also be administered in combination with an agent that is an inhibitor of HCV NS3 serine protease. HCV NS3 serine protease is an essential viral enzyme and has been described to be an excellent target for inhibition of HCV replication. Both substrate and non-substrate based inhibitors of HCV NS3 protease inhibitors are  
10 disclosed in WO 98/22496, WO 98/46630, WO 99/07733, WO 99/07734, WO 99/38888, WO 99/50230, WO 99/64442, WO 00/09543, WO 00/59929, and GB-2337262. HCV NS3 protease as a target for the development of inhibitors of HCV replication and for the treatment of HCV infection is discussed in B.W. Dymock, “Emerging therapies for hepatitis C virus infection,” Emerging Drugs, 6: 13-42  
15 (2001).

Ribavirin, levovirin, and viramidine may exert their anti-HCV effects by modulating intracellular pools of guanine nucleotides via inhibition of the intracellular enzyme inosine monophosphate dehydrogenase (IMPDH). IMPDH is the rate-limiting enzyme on the biosynthetic route in *de novo* guanine nucleotide biosynthesis. Ribavirin is readily phosphorylated intracellularly and the monophosphate derivative is an inhibitor of IMPDH. Thus, inhibition of IMPDH represents another useful target for the discovery of inhibitors of HCV replication. Therefore, the compounds of the present invention may also be administered in combination with an inhibitor of IMPDH, such as VX-497, which is disclosed in WO 97/41211 and WO 01/00622 (assigned to Vertex); another IMPDH inhibitor, such as that disclosed in WO 00/25780 (assigned to Bristol-Myers Squibb); or mycophenolate mofetil [see A.C. Allison and E.M. Eugui, Agents Action, 44 (Suppl.): 165 (1993)].

For the treatment of HCV infection, the compounds of the present invention may also be administered in combination with the antiviral agent  
30 amantadine (1-aminoadamantane) [for a comprehensive description of this agent, see J. Kirschbaum, Anal. Profiles Drug Subs. 12: 1-36 (1983)].

The compounds of the present invention may also be combined for the treatment of HCV infection with antiviral 2'-C-branched ribonucleosides disclosed in R. E. Harry-O'kuru, et al., J. Org. Chem., 62: 1754-1759 (1997); M. S. Wolfe, et al.,  
35 Tetrahedron Lett., 36: 7611-7614 (1995); U.S. Patent No. 3,480,613 (Nov. 25, 1969);

International Publication Number WO 01/90121 (29 November 2001); International Publication Number WO 01/92282 (6 December 2001); and International Publication Number WO 02/32920 (25 April 2002); the contents of each of which are incorporated by reference in their entirety. Such 2'-C-branched ribonucleosides 5 include, but are not limited to, 2'-C-methyl-cytidine, 2'-C-methyl-uridine, 2'-C-methyl-adenosine, 2'-C-methyl-guanosine, and 9-(2-C-methyl-β-D-ribofuranosyl)-2,6-diaminopurine.

By "pharmaceutically acceptable" is meant that the carrier, diluent, or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. 10

Also included within the present invention are pharmaceutical compositions comprising the carbocyclic nucleoside compounds and derivatives thereof of the present invention in association with a pharmaceutically acceptable carrier. Another example of the invention is a pharmaceutical composition made by 15 combining any of the compounds described above and a pharmaceutically acceptable carrier. Another illustration of the invention is a process for making a pharmaceutical composition comprising combining any of the compounds described above and a pharmaceutically acceptable carrier.

Also included within the present invention are pharmaceutical 20 compositions useful for inhibiting RNA-dependent RNA viral polymerase in particular HCV NS5B polymerase comprising an effective amount of a compound of the present invention and a pharmaceutically acceptable carrier. Pharmaceutical compositions useful for treating RNA-dependent RNA viral infection in particular HCV infection are also encompassed by the present invention as well as a method of 25 inhibiting RNA-dependent RNA viral polymerase in particular HCV NS5B polymerase and a method of treating RNA-dependent viral replication and in particular HCV replication. Additionally, the present invention is directed to a pharmaceutical composition comprising a therapeutically effective amount of a compound of the present invention in combination with a therapeutically effective 30 amount of another agent active against RNA-dependent RNA virus and in particular against HCV. Agents active against HCV include, but are not limited to, ribavirin, levovirin, viramidine, thymosin alpha-1, an inhibitor of HCV NS3 serine protease, interferon- $\alpha$ , pegylated interferon- $\alpha$  (peginterferon- $\alpha$ ), a combination of interferon- $\alpha$  and ribavirin, a combination of peginterferon- $\alpha$  and ribavirin, a combination of 35 interferon- $\alpha$  and levovirin, and a combination of peginterferon- $\alpha$  and levovirin.

Interferon- $\alpha$  includes, but is not limited to, recombinant interferon- $\alpha$ 2a (such as Roferon interferon available from Hoffmann-LaRoche, Nutley, NJ), interferon- $\alpha$ 2b (such as Intron-A interferon available from Schering Corp., Kenilworth, NJ), a consensus interferon, and a purified interferon- $\alpha$  product. For a discussion of 5 ribavirin and its activity against HCV, see J.O. Saunders and S.A. Raybuck, "Inosine Monophosphate Dehydrogenase: Consideration of Structure, Kinetics, and Therapeutic Potential," Ann. Rep. Med. Chem., 35: 201-210 (2000).

Another aspect of the present invention provides for the use of the carbocyclic nucleoside compounds and derivatives thereof and their pharmaceutical 10 compositions for the manufacture of a medicament for the inhibition of RNA-dependent RNA viral replication, in particular HCV replication, and/or the treatment of RNA-dependent RNA viral infection, in particular HCV infection. Yet a further aspect of the present invention provides for the carbocyclic nucleoside compounds and derivatives thereof and their pharmaceutical compositions for use as a 15 medicament for the inhibition of RNA-dependent RNA viral replication, in particular HCV replication, and/or for the treatment of RNA-dependent RNA viral infection, in particular HCV infection.

The pharmaceutical compositions of the present invention comprise a compound of structural formula I as an active ingredient or a pharmaceutically 20 acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients.

The compositions include compositions suitable for oral, rectal, topical, parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (nasal or buccal inhalation), or nasal administration, 25 although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

In practical use, the compounds of structural formula I can be 30 combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be 35 employed, such as, for example, water, glycols, oils, alcohols, flavoring agents,

preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for 5 example, powders, hard and soft capsules and tablets, with the solid oral preparations being preferred over the liquid preparations.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard 10 aqueous or nonaqueous techniques. Such compositions and preparations should contain at least 0.1 percent of active compound. The percentage of active compound in these compositions may, of course, be varied and may conveniently be between about 2 percent to about 60 percent of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that an effective dosage 15 will be obtained. The active compounds can also be administered intranasally as, for example, liquid drops or spray.

The tablets, pills, capsules, and the like may also contain a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a 20 lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, 25 sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

Compounds of structural formula I may also be administered parenterally. Solutions or suspensions of these active compounds can be prepared in 30 water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile 35 aqueous solutions or dispersions and sterile powders for the extemporaneous

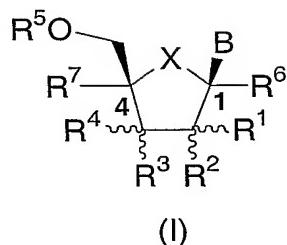
preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier 5 can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

Any suitable route of administration may be employed for providing a mammal, especially a human with an effective dosage of a compound of the present 10 invention. For example, oral, rectal, topical, parenteral, ocular, pulmonary, nasal, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like. Preferably compounds of structural formula I are administered orally.

For oral administration to humans, the dosage range is 0.01 to 1000 15 mg/kg body weight in divided doses. In one embodiment the dosage range is 0.1 to 100 mg/kg body weight in divided doses. In another embodiment the dosage range is 0.5 to 20 mg/kg body weight in divided doses. For oral administration, the compositions are preferably provided in the form of tablets or capsules containing 1.0 to 1000 milligrams of the active ingredient, particularly, 1, 5, 10, 15, 20, 25, 50, 75, 20 100, 150, 200, 250, 300, 400, 500, 600, 750, 800, 900, and 1000 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated.

The effective dosage of active ingredient employed may vary 25 depending on the particular compound employed, the mode of administration, the condition being treated and the severity of the condition being treated. Such dosage may be ascertained readily by a person skilled in the art. This dosage regimen may be adjusted to provide the optimal therapeutic response.

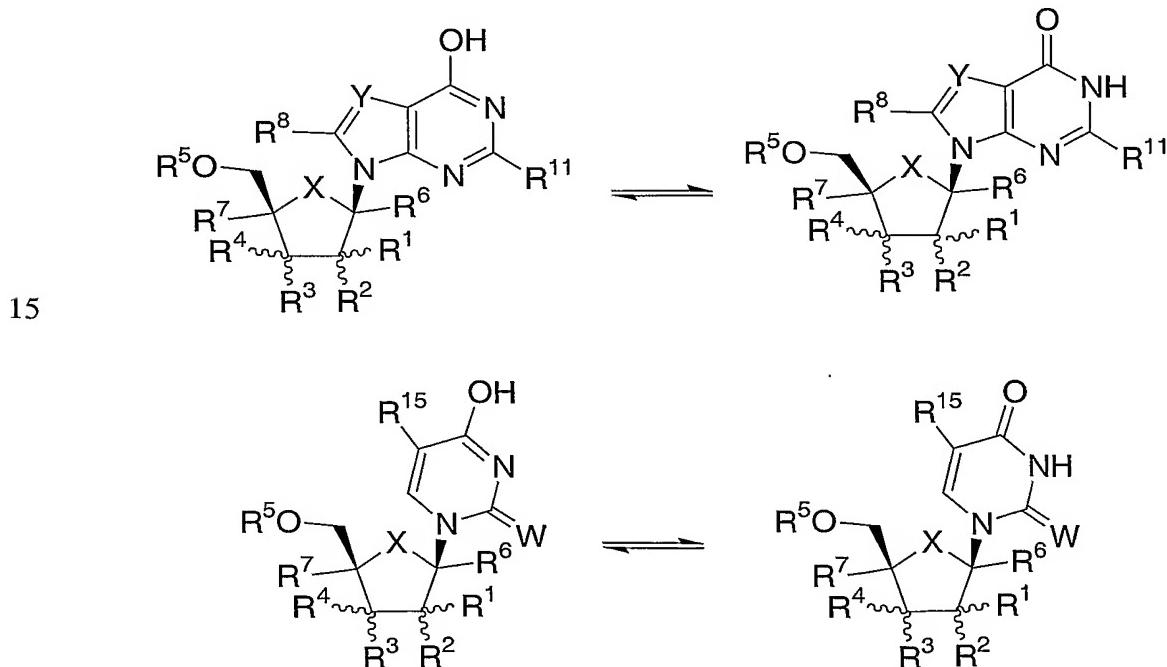
The compounds of the present invention contain one or more 30 asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. The present invention is meant to comprehend carbocyclic nucleoside compounds having the stereochemical configuration for the five-membered carbocycle depicted in the structural formula below, that is, carbocyclic nucleoside compounds in which the substituents at the positions denoted as 1 and 4 in the formula below have a *cis* 35 relative configuration.



The stereochemistry of the R<sup>1</sup>-R<sup>4</sup> substituents on the cyclopentane ring of the compounds of the present invention of structural formula I above is denoted by squiggly lines which signifies that substituents R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> can have either the α (substituent “down”) or β (substituent “up”) configuration independently of one another.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

Some of the compounds described herein may exist as tautomers such as keto-enol tautomers. The individual tautomers as well as mixtures thereof are encompassed with compounds of structural formula I. Example of keto-enol tautomers which are intended to be encompassed within the compounds of the present invention are illustrated below:



Compounds of structural formula I may be separated into their individual diastereoisomers by, for example, fractional crystallization from a suitable solvent, for example methanol or ethyl acetate or a mixture thereof, or via chiral chromatography using an optically active stationary phase.

5           Alternatively, any stereoisomer of a compound of the structural formula I may be obtained by stereospecific synthesis using optically pure starting materials or reagents of known configuration.

The compounds of the present invention may be administered in the form of a pharmaceutically acceptable salt. The term "pharmaceutically acceptable salt" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts of basic compounds encompassed within the term "pharmaceutically acceptable salt" refer to non-toxic salts of the compounds of this invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid.

10          Representative salts of basic compounds of the present invention include, but are not limited to, the following: acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide,

15          hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, oleate, oxalate, pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, sulfate, subacetate, succinate, tannate, tartrate,

20          teoclate, tosylate, triethiodide and valerate. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof include, but are not limited to, salts derived from inorganic bases including aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganese, mangamous, potassium, sodium, zinc, and the like. Particularly preferred are the

25          ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, cyclic amines, and basic ion-exchange resins, such as arginine, betaine, caffeine, choline, N,N-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-

30          ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine,

35          ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine,

isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

Also, in the case of a carboxylic acid (-COOH) or alcohol group being present in the compounds of the present invention, pharmaceutically acceptable esters of carboxylic acid derivatives, such as methyl, ethyl, or pivaloyloxymethyl, or acyl derivatives of alcohols, such as acetate, octanoate, or maleate, can be employed. Included are those esters and acyl groups known in the art for modifying the solubility or hydrolysis characteristics for use as sustained-release or prodrug formulations.

10

Preparation of the Compounds of the Invention

The compounds of the present invention can be prepared following modifications of procedures described by Bindu Madhavan et al. in J. Org. Chem., 51: 1287-1293 (1986) and J. Med. Chem., 31: 1798-1804 (1988) as well as synthetic methodologies well-established in the practice of nucleoside and nucleotide chemistry, as described in "Chemistry of Nucleosides and Nucleotides," L.B. Townsend, ed., Vols. 1-3, Plenum Press, 1988, which is incorporated by reference herein in its entirety.

20

Abbreviations Used in the Description of the Preparation of the Compounds of the Present Invention:

BCl <sub>3</sub>	Boron trichloride
BOM-Cl	Benzyl chloromethyl ether
BuLi	n-Butyl lithium
CH <sub>2</sub> Cl <sub>2</sub>	Dichloromethane
DCC	1,3-Dicyclohexylcarbodiimide
DIPEA	N,N-Diisopropylethylamine
DMA	N,N-Dimethylacetamide
DMF	N,N-Dimethylformamide
DMSO	Dimethyl sulfoxide
ESMS	Electrospray mass spectrum
EtOAc	Ethyl acetate
HPLC	High-performance liquid chromatography
LiBH <sub>4</sub>	Lithium borohydride
LAH	Lithium aluminum hydride
MCPBA	meta-Chloroperbenzoic acid
MMT	p-Methoxyphenyldiphenylmethyl (p-anisyldiphenylmethyl)
MS	Mass spectral
NMR	Nuclear magnetic resonance
POCl <sub>3</sub>	Phosphorus oxychloride
TDA-1	Tris[2-(2-methoxyethoxy)ethyl]amine
THF	Tetrahydrofuran
TIPDS	(1,1,3,3-Tetraisopropyldisiloxanylidene)
TLC	Thin-layer chromatography
TREATHF	Triethylamine trihydrofluoride

Reaction Schemes A-B illustrate the methods employed in the synthesis of the compounds of the present invention of structural formula I. All substituents are as defined above unless indicated otherwise.

5           A representative general method for the preparation of compounds of the present invention wherein X is C=CH<sub>2</sub> is outlined in Scheme A below. This Scheme illustrates the synthesis of compounds of the present invention of structural formula A-5. The starting material is the known oxirane of structural formula A-1, whose synthesis has been described in J. Med. Chem., 31: 1798-1804 (1988). The carbocyclic “nucleosidic” linkage is constructed by opening of the oxirane in A-1 with

10

the metal salt (such as lithium, sodium, or potassium) of an appropriately substituted purine or 7-deaza-purine A-6, such as an appropriately substituted 4-halo-1*H*-pyrrolo[2,3-*d*]pyrimidine, which can be generated *in situ* by treatment with an alkali hydride (such as sodium hydride), an alkali hydroxide (such as potassium hydroxide),

5 an alkali carbonate (such as potassium carbonate), or an alkali hexamethyldisilazide (such as NaHMDS) in a suitable anhydrous organic solvent, such as acetonitrile, tetrahydrofuran, 1-methyl-2-pyrrolidinone, N,N-dimethylformamide (DMF) or N,N-dimethylacetamide (DMA). The ring-opening reaction can be catalyzed by using a phase-transfer catalyst, such as TDA-1 or triethylbenzylammonium chloride, in a

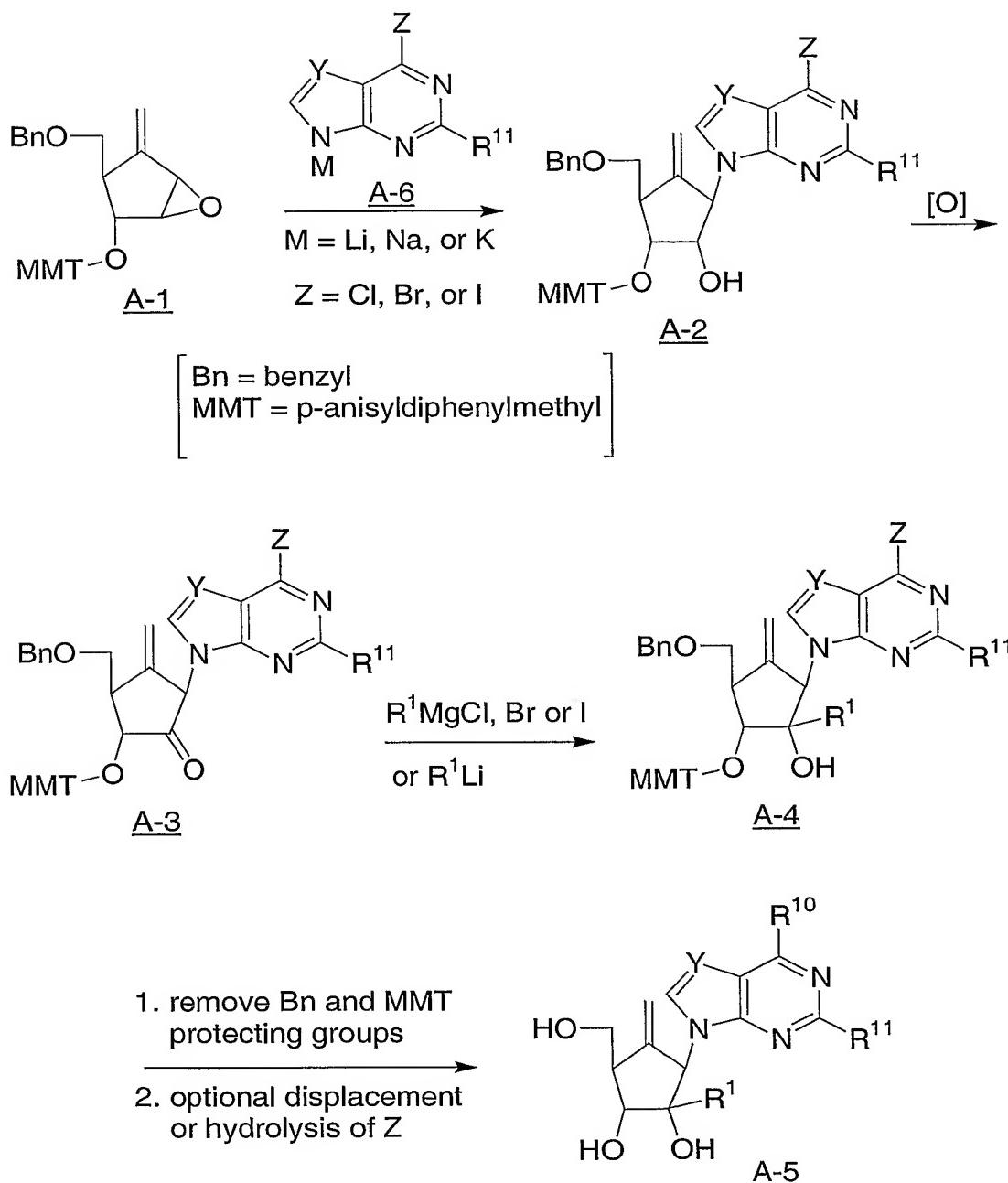
10 two-phase system (solid-liquid or liquid-liquid). The cyclopentanol hydroxyl group in A-2 is then oxidized with a suitable oxidizing agent, such as a chromium trioxide or chromate reagent, Dess-Martin periodinane, or by Swern oxidation, to afford a cyclopentanone of structural formula A-3. Addition of a Grignard reagent, such as an alkyl, alkenyl, or alkynyl magnesium halide (for example, MeMgBr, EtMgBr,

15 vinylMgBr, allylMgBr, and ethynylMgBr) or an alkyl, alkenyl, or alkynyl lithium, such as MeLi, across the carbonyl double bond of A-3 in a suitable organic solvent, such as tetrahydrofuran, diethyl ether, and the like, affords the tertiary cyclopentanol of structural formula A-4. The optional protecting groups in the protected carbocyclic nucleoside of structural formula A-4 are then cleaved following established

20 deprotection methodologies, such as those described in T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis," 3<sup>rd</sup> ed., John Wiley & Sons, 1999. Optional introduction of an amino group at the 4-position of the 7-deaza-purine nucleus (or 6-position of a purine nucleus) is effected by treatment of a 4-halo intermediate A-5 (Z = Cl, Br, or I) with the appropriate amine, such as alcoholic

25 ammonia or liquid ammonia, to generate a primary amine at the C-4 position (-NH<sub>2</sub>), an alkylamine to generate a secondary amine (-NHR), or a dialkylamine to generate a tertiary amine (-NRR'). A 7*H*-pyrrolo[2,3-*d*]pyrimidin-4(3*H*)one or 1,9-dihydro-6*H*-purin-6-one compound may be derived by hydrolysis of A-5 (Z = Cl, Br, or I) with aqueous base, such as aqueous sodium hydroxide. Alcoholysis (such as methanolysis)

30 of A-5 (Z = Cl, Br, or I) affords a C-4 alkoxide (-OR), whereas treatment with an alkyl mercaptide affords a C-4 alkylthio (-SR) derivative. Subsequent chemical manipulations well-known to practitioners of ordinary skill in the art of organic/medicinal chemistry may be required to attain the desired compounds of the present invention.

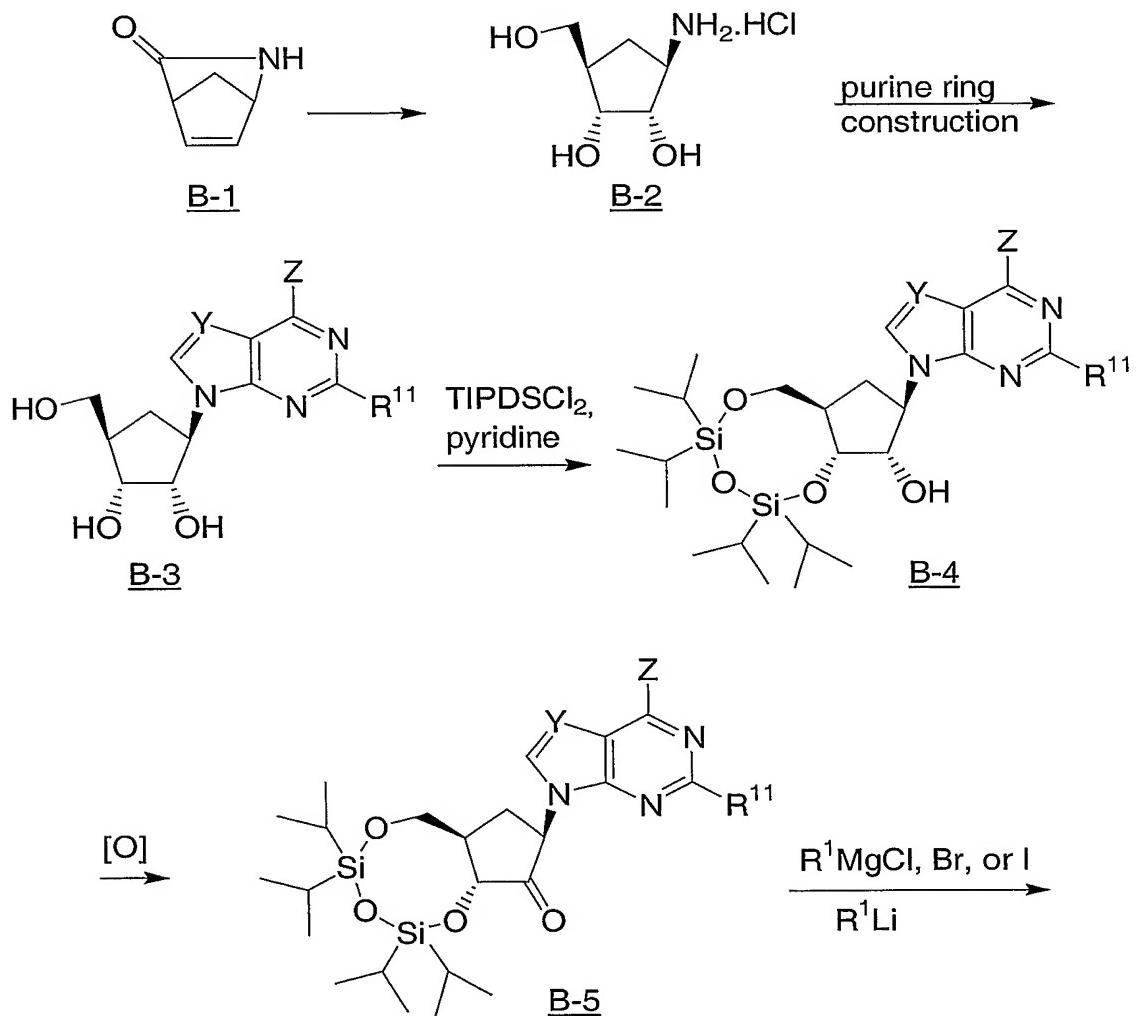
Scheme A

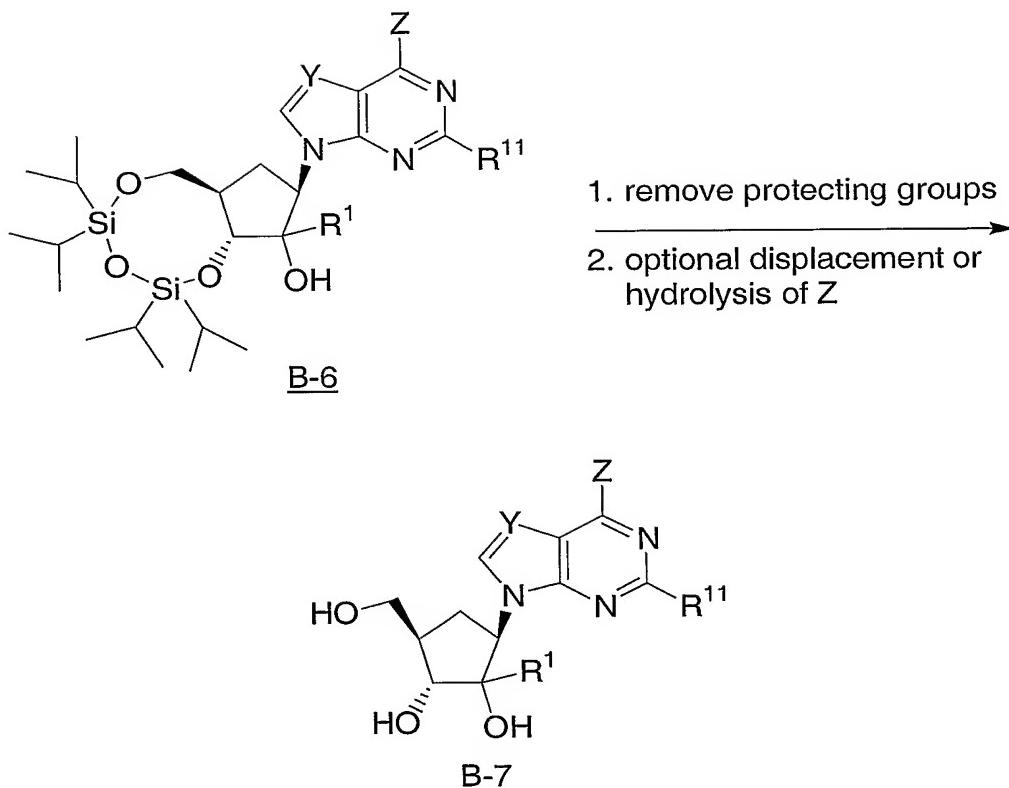
A representative general method for the preparation of compounds of  
5 the present invention wherein X is  $CH_2$  is outlined in Scheme B below. This Scheme

illustrates the synthesis of compounds of the present invention of structural formula B-7. A useful starting material is the aminocyclopentanetriol of structural formula B-2, which is prepared from commercially available (1R)-(-)-2-azabicyclo[2.2.1]hept-5-en-3-one (B-1) in a similar fashion as that described in *J. Org. Chem.*, 46: 3268  
5 for the preparation of the corresponding racemic form. Elaboration of the amino functionality in B-2 into a substituted purine or 7-deaza-purine is carried out by methods analogous to those described in *J. Med. Chem.*, 27: 534 (1984); *J. Org. Chem.*, 51: 1289 (1986); and *J. Med. Chem.*, 31: 1798 (1988); and references cited therein. The 1,3-diol in the derived intermediate B-3 is protected in the form of its  
10 (1,1,3,3-tetraisopropylsiloxylidene) (TIPDS) derivative B-4. The cyclopentanol hydroxyl group in B-4 is then oxidized with a suitable oxidizing agent, such as a chromium trioxide or chromate reagent, Dess-Martin periodinane, or by Swern oxidation, to afford a cyclopentanone of structural formula B-5. Addition of a Grignard reagent, such as an alkyl, alkenyl, or alkynyl magnesium halide (for  
15 example, MeMgBr, EtMgBr, vinylMgBr, allylMgBr, and ethynylMgBr) or an alkyl, alkenyl, or alkynyl lithium, such as MeLi, across the carbonyl double bond of B-5 in a suitable organic solvent, such as tetrahydrofuran, diethyl ether, and the like, affords the tertiary cyclopentanol of structural formula B-6. The TIPDS protecting group in the protected carbocyclic nucleoside of structural formula B-6 is then cleaved  
20 following established deprotection methodologies, such as by treatment with tetrabutylammonium fluoride in THF or triethylamine dihydrogen fluoride in THF. Optional introduction of an amino group at the 4-position of the 7-deaza-purine nucleus (or 6-position of a purine nucleus) is effected by treatment of a 4-halo intermediate B-7 (Z = Cl, Br, or I) with the appropriate amine, such as alcoholic  
25 ammonia or liquid ammonia, to generate a primary amine at the C-4 position (-NH<sub>2</sub>), an alkylamine to generate a secondary amine (-NHR), or a dialkylamine to generate a tertiary amine (-NRR'). A 7*H*-pyrrolo[2,3-*d*]pyrimidin-4(3*H*)one or 1,9-dihydro-6*H*-purin-6-one compound may be derived by hydrolysis of B-7 (Z = Cl, Br, or I) with aqueous base, such as aqueous sodium hydroxide. Alcoholsysis (such as methanolysis)  
30 of B-7 (Z = Cl, Br, or I) affords a C-4 alkoxide (-OR), whereas treatment with an alkyl mercaptide affords a C-4 alkylthio (-SR) derivative. Subsequent chemical manipulations well-known to practitioners of ordinary skill in the art of organic/medicinal chemistry may be required to attain the desired compounds of the present invention. Mixtures of diastereoisomers at the stereogenic tertiary alcohol

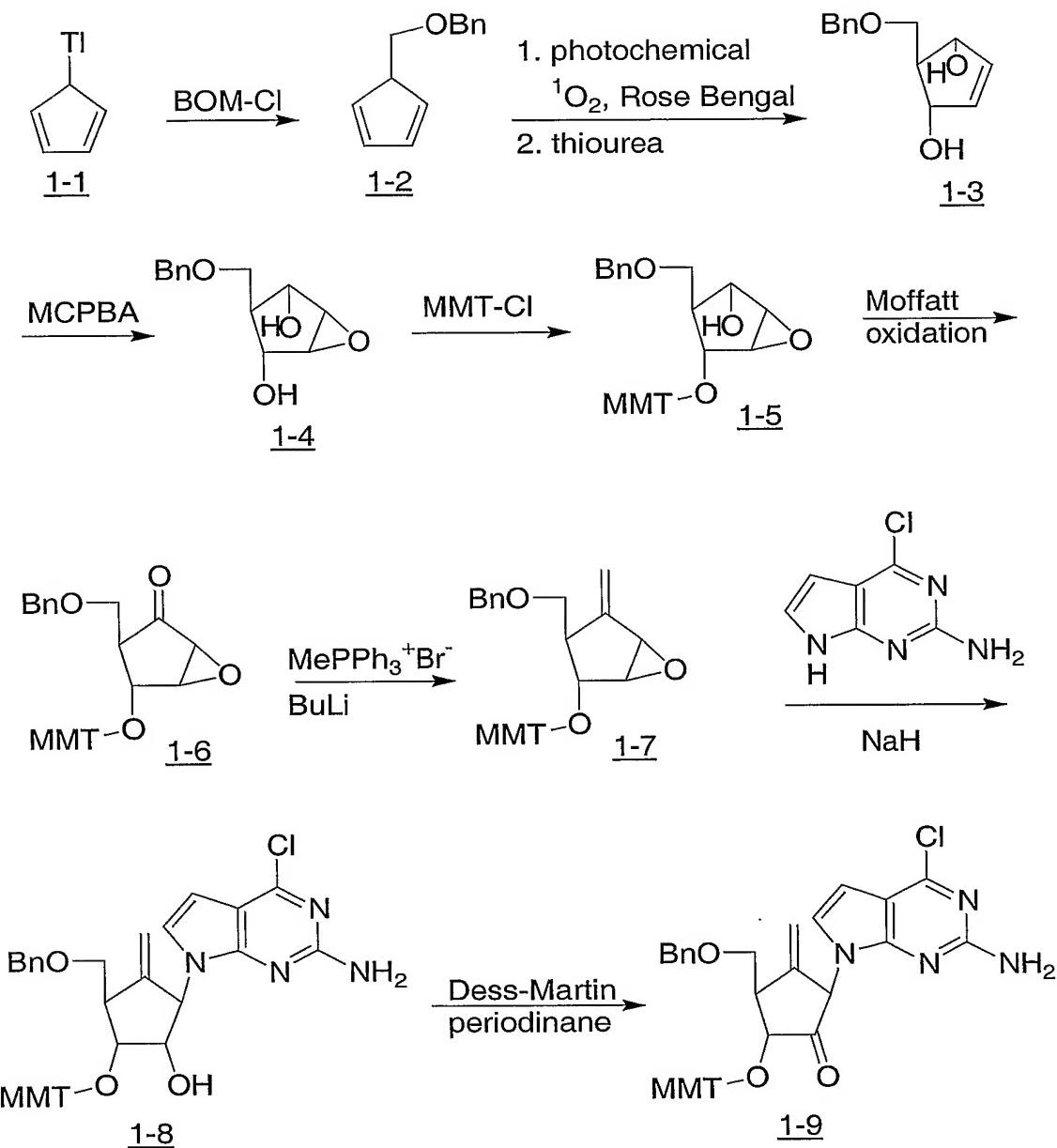
center in B-7 may be resolved by chromatographic methods, such as HPLC on a suitable solid support.

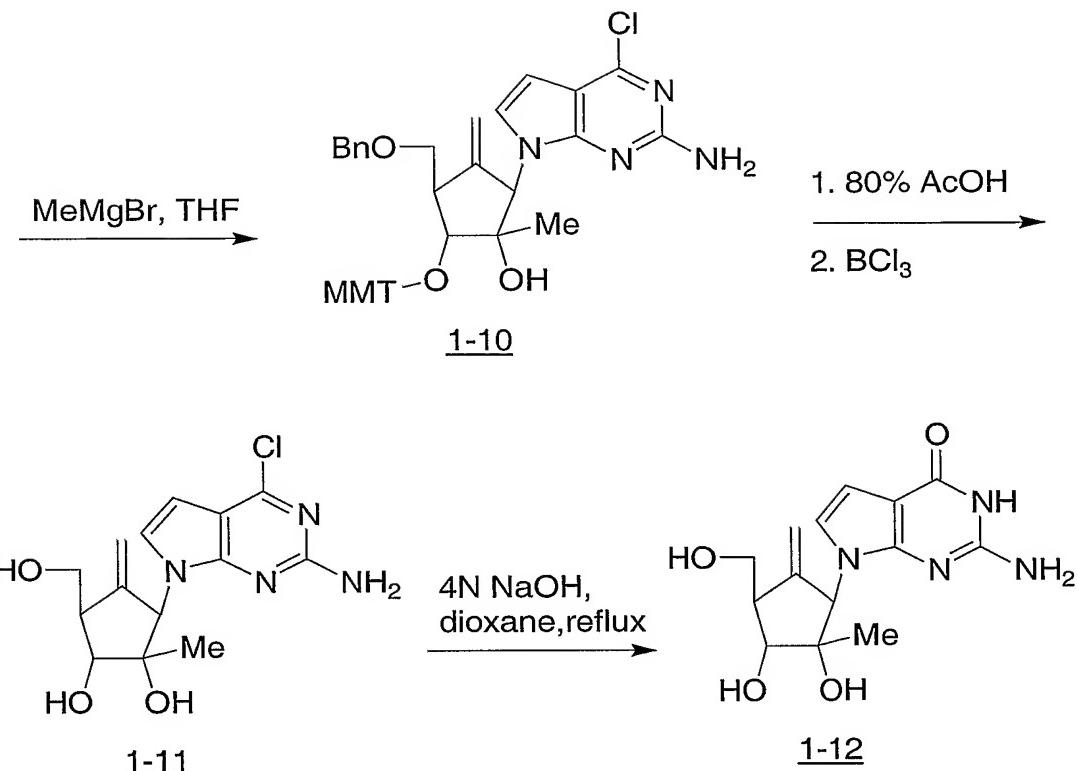
Scheme B





The examples below provide citations to literature publications, which contain details for the preparation of intermediates employed in the preparation of final compounds of the present invention. The compounds of the present invention were prepared according to procedures detailed in the following examples. The examples are not intended to be limitations on the scope of the instant invention in any way, and they should not be so construed. Those skilled in the art of organic synthesis will readily appreciate that known variations of the conditions and processes of the following preparative procedures can be used to prepare these and other compounds of the present invention. All temperatures are degrees Celsius unless otherwise noted.

Scheme 1

EXAMPLE 1

5    ( $\pm$ )-2-Amino-7-[ $(1\beta,2\alpha$ OH, $3\alpha,4\beta$ )-2,3-dihydroxy-4-hydroxymethyl-2-methyl-5-methylene-cyclopentyl]-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (1-12)

Step A:      ( $1\alpha,2\beta,3\alpha$ )-2-(Benzylloxymethyl)-cyclopent-4-ene-1,3-diol (1-3)

Compound 1-3 was synthesized by modification of the procedure of  
10   Bindu Madhavan, G.V. et al., in *J. Org. Chem.* 51: 1287-1293 (1986). Benzyl  
chloromethyl ether (BOM-Cl) (90%, 23.8 mL, 154.61 mmol) was added dropwise to a  
vigorously stirred suspension of cyclopentadienyl thallium (50 g, 185.53 mmol) in 50  
mL of anhydrous diethyl ether at -20 °C. The resulting mixture was then stirred at -  
20 °C for 24 h. The mixture was filtered through a fritted funnel pre-cooled to -20 °C  
15   into a pre-cooled round-bottom flask. The excess benzyl chloromethyl ether and the  
solvent were removed by evaporation under diminished pressure at -10 °C. The  
residue was dissolved in pre-cooled (-20 °C) methanol (100 mL). The resulting  
solution was added to a solution of Rose Bengal (316 mg), sodium acetate (732 mg),  
and thiourea (13.26 g) in 500 mL of methanol which had been pre-saturated with

oxygen and cooled to -10 °C. The reaction vessel was illuminated with two 100-watt flood lamps and stirred at -10 °C for 24 h with continuous bubbling of oxygen. The solvent was then removed by evaporation under diminished pressure and the residue taken up in ethyl acetate (1500 mL). The ethyl acetate solution was washed twice 5 with water (1000 mL) and dried over anhydrous sodium sulfate. The solvent was removed by evaporation under diminished pressure and the residue purified by flash chromatography on silica gel (first using a 7:2:1 dichloromethane/acetone/hexane system and then 2:1 ethyl acetate/hexane system as eluant). The fractions containing the product were concentrated under diminished pressure to give the title compound 10 1-3 (7 g), whose proton and C-13 NMR spectral data were identical to those given in the Bindu Madhavan publication.

Step B:      (1 $\alpha$ ,2 $\alpha$ ,3 $\beta$ ,4 $\alpha$ ,5 $\alpha$ )-3-(Benzylloxymethyl)-6-oxabicyclo[3.1.0]hexane-2,4-diol (1-4)

15                Compound 1-3 from Step A (2.0 g, 9.1 mmol) was dissolved in 50 mL of dichloromethane and cooled to 0 °C. To this was added *meta*-chloroperoxybenzoic acid (MCPBA) (77%, 3.5 g, 15.64 mmol) in portions. The resulting solution was stirred at room temperature for 2 d at which point the product and *meta*-chlorobenzoic acid precipitated out. The solvent was removed by evaporation under diminished 20 pressure, and the resulting crude product was purified by flash chromatography on silica gel using 3:1 ethyl acetate/hexanes as eluant to afford the title compound 1-4 (2.15 g), whose proton and C-13 NMR spectral data were identical to those given in *J. Org. Chem.* 51: 1287-1293 (1986).

25                Step C:      ( $\pm$ )-(1 $\alpha$ ,2 $\alpha$ ,3 $\beta$ ,4 $\alpha$ ,5 $\alpha$ )-(3-(Benzylloxymethyl)-4-(p-anisyldiphenylmethoxy)-6-oxabicyclo[3.1.0]hexan-2-ol (1-5)  
A solution of 1-4 (260 mg, 1.1 mmol) and p-anisylchlorodiphenylmethane (460 mg, 1.49 mmol) in anhydrous pyridine (6.5 mL) was stirred under argon at room temperature for 2 d. Excess pyridine was removed by 30 evaporation under diminished pressure. The residue was taken up in ethyl acetate (30 mL), washed twice with water (20 mL), twice with saturated sodium bicarbonate solution, and dried over anhydrous sodium sulfate. The solvent was removed by evaporation under diminished pressure and the residue purified by flash chromatography on silica gel using 4:1 hexane/ethyl acetate as eluant to give the title

compound 1-5 (260 mg), whose proton and carbon-13 NMR spectral data matched those given in Bindu Madhavan, G.V. et al., *J. Med. Chem.*, 31: 1798-1804 (1988).

Step D: (±)-(1 $\alpha$ ,3 $\beta$ ,4 $\alpha$ ,5 $\alpha$ )-3-(Benzylloxymethyl)-4-(p-anisyldiphenylmethoxy)-6-oxa-bicyclo[3.1.0]hexan-2-one (1-6)

Methylphosphonic acid (7 mg, 0.05 mmol) was added to a solution of 1-5 (260 mg, 0.52 mmol) and 1,3-dicyclohexylcarbodiimide (420 mg, 2.03 mmol) in methylsulfoxide (2.5 mL) cooled to 0 °C. After the mixture had stirred at room temperature for 16 h, a solution of oxalic acid (335 mg in 3.35 mL of water) was added and stirring was continued for an additional 2 h. The mixture was filtered and the filtrate diluted with ethyl acetate (30 mL). The resulting solution was extracted three times with brine (10 mL). The ethyl acetate layer was dried over anhydrous sodium sulfate and evaporated under diminished pressure. The residue was purified by flash chromatography on silica gel using 4:1 hexane/ethyl acetate as eluant to give the title compound 1-6 (135 mg), whose proton and carbon-13 NMR spectral data matched those given in Bindu Madhavan, G.V. et al., *J. Med. Chem.*, 31: 1798-1804 (1988).

Step E: (±)-(1 $\alpha$ ,2 $\alpha$ ,3 $\beta$ ,5 $\alpha$ )-3-(Benzylloxymethyl)-2-(p-anisyldiphenylmethoxy)-4-methylene-6-oxa-bicyclo[3.1.0]hexane (1-7)

To a solution of methyltriphenylphosphonium bromide (193 mg, 0.54 mmol) in anhydrous THF (2.66 mL) at -78 °C under argon was added n-butyllithium (0.375 mL of a 1.6 M solution in hexanes, 0.6 mmol). The solution was allowed to come to room temperature, stirred for 20 min, and then re-cooled to -78 °C. To this mixture was added a solution of 1-6 (135 mg, 0.27 mmol) in 1.5 mL THF. The resulting solution was allowed to come to room temperature and stirred overnight. The reaction mixture was diluted with water (30 mL) and extracted three times with diethyl ether (60 mL). The combined ether extracts were dried over anhydrous sodium sulfate and evaporated under diminished pressure. The residue was purified by flash chromatography on silica gel using 5:1 hexanes/ethyl acetate as eluant to give title compound 1-7 (130 mg), whose proton and carbon-13 NMR spectral data matched those given in Bindu Madhavan, G.V. et al., *J. Med. Chem.* 1988, 31, 1798-1804.

Step F: (±)-(1 $\alpha$ ,2 $\beta$ ,4 $\beta$ ,5 $\alpha$ )-2-(2-Amino-4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-4-(benzyloxymethyl)-5-(p-anisyldiphenylmethoxy)-3-methylenecyclopentanol (1-8)

Sodium hydride (14.4 mg of a 60% suspension, 0.36 mmol) and 2-amino-4-chloro-7*H* pyrrolo[2,3-*d*]pyrimidine (62 mg, 0.36 mmol) were dissolved in anhydrous DMF (5 mL) and stirred at 120 °C for 15 min. A solution of 1-7 in 1 mL DMF was added and the reaction was stirred overnight under argon at 120 °C. The solvent was evaporated under diminished pressure and the residue was taken up in dichloromethane (20 mL). The organic layer was washed twice with water (15 mL) and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed by evaporation under diminished pressure and the residue purified by flash chromatography on silica gel using 1:1 hexanes/EtOAc as eluant to give 25 mg of title compound 1-8 as a white foam.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.2-7.6 (m, 17H), 6.8 (m, 4H), 6.2 (d, 1H), 5.49 (d, 1H), 4.27 (s, 2H), 4.08 (d, 1H), 3.75 (s, 3H), 3.4 (br, 2H), 3.2 (br, 1H).

Step G: (±)-(2 $\beta$ ,4 $\beta$ ,5 $\alpha$ )-2-(2-Amino-4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-4-(benzyloxymethyl)-5-(p-anisyldiphenylmethoxy)-3-methylenecyclopentanone (1-9)

Compound 1-8 (1 eq) is oxidized by dissolving it in anhydrous dichloromethane and adding the solution to an ice-cold suspension of Dess Martin periodinane (4 eq) in anhydrous dichloromethane under argon. The solution after stirring at room temperature for 4 d is diluted with ethyl acetate and poured into a solution of sodium thiosulfate in saturated sodium bicarbonate solution. The organic layer is separated and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The residue is purified by flash chromatography on a silica gel column to give the title compound 1-9.

Step H: (±)-(1 $\alpha$ OH,2 $\beta$ ,4 $\beta$ ,5 $\alpha$ )-2-(2-Amino-4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-(4-benzyloxymethyl)-5-(p-anisyldiphenylmethoxy)-1-methyl-3-methylenecyclopentanol (1-10)

Compound 1-9 from Step G is dissolved in anhydrous THF and the solution is added to a solution of methylmagnesium bromide (4 eq) in anhydrous THF at -78 °C. The resulting mixture is stirred overnight at -70 °C to -50 °C. The reaction mixture is quenched with saturated NH<sub>4</sub>Cl solution and the resulting slurry filtered through a pad of celite. The residue is washed with ethyl acetate and the combined

filtrate and washings are transferred to a separatory funnel. After separating the organic layer, it is washed with saturated aqueous NH<sub>4</sub>Cl solution followed by water and then brine. After drying the organic layer over anhydrous Na<sub>2</sub>SO<sub>4</sub>, the filtrate is evaporated under diminished pressure followed by purification of the residue by flash chromatography on silica gel to furnish the title compound 1-10.

5      Step I:     (±)-(1αOH,2α,3β,5β)-5-(2-Amino-4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-3-(benzyloxymethyl)-1-methyl-4-methylenecyclopentane-1,2-diol

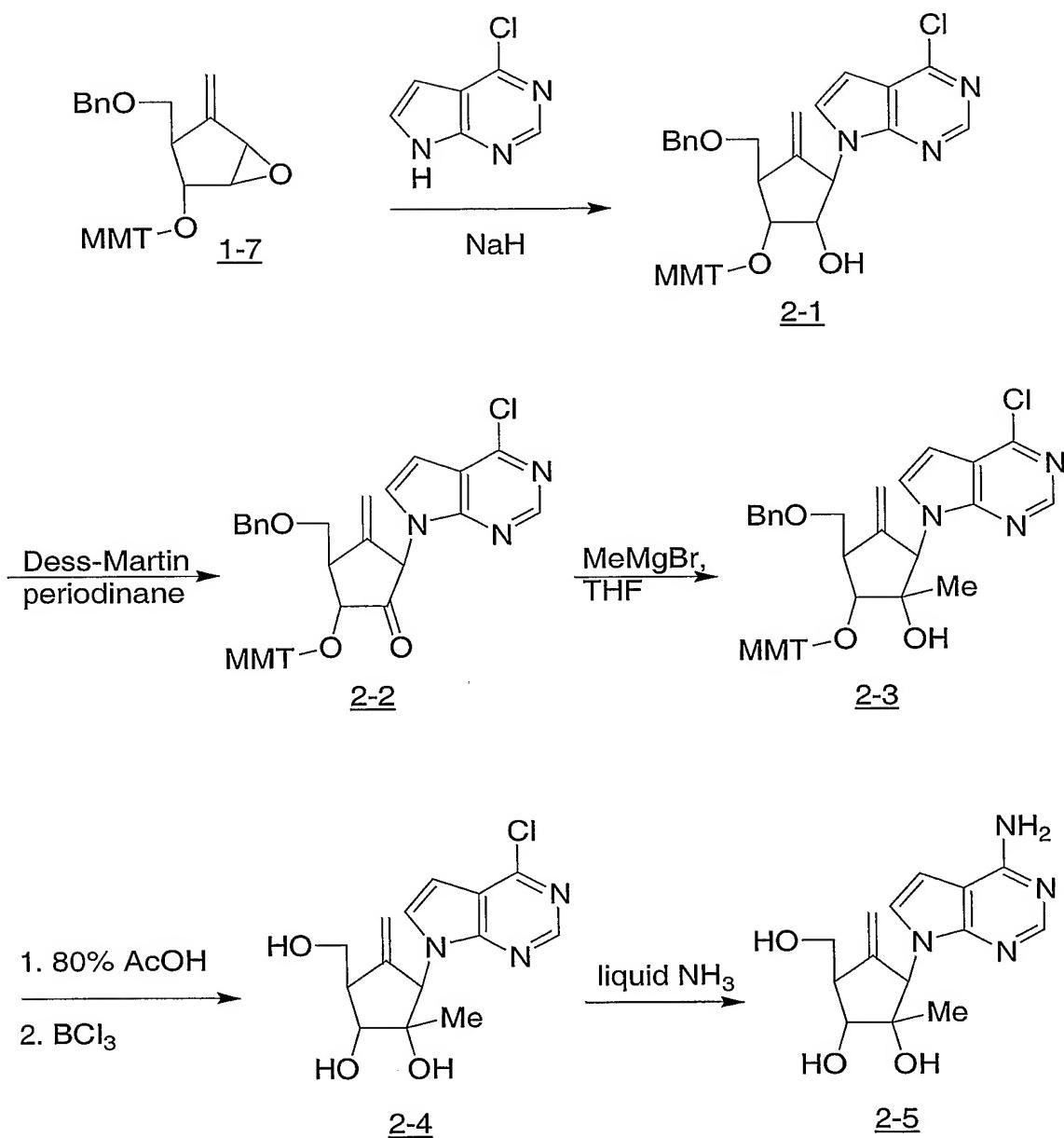
10     This compound is prepared by dissolving compound 1-10 in 80% acetic acid and stirring overnight. The solvent is removed by evaporation under diminished pressure and the residue coevaporated twice with toluene. The residue is purified by chromatography on silica gel to furnish the title compound.

15     Step J:     (±)-(1αOH,2α,3β,5β)-5-(2-Amino-4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-3-(hydroxymethyl)-1-methyl-4-methylenecyclopentane-1,2-diol (1-11)

20     This compound is prepared by treating a solution of the compound from Step I in anhydrous dichloromethane with boron trichloride at -70 °C for several h. The reaction is quenched with ammonia in methanol and the solvents are removed by evaporation under diminished pressure. Purification of the residue on a silica gel column affords the desired product 1-11.

25     Step K:     (±)-2-Amino-7-[(1β,2αOH,3α,4β)-2,3-dihydroxy-4-hydroxymethyl-2-methyl-5-methylene-cyclopentyl]-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one (1-12)

30     The title compound is obtained from compound 1-11 by dissolving it in 1,4-dioxane and treating the solution with 4N NaOH at reflux temperature for several h. After cooling to room temperature, the reaction mixture is neutralized with 4N HCl, the mixture evaporated and the crude product purified by silica gel chromatography.

Scheme 2

( $\pm$ )-(1 $\alpha$ OH,2 $\alpha$ ,3 $\beta$ ,5 $\beta$ )-5-(4-Amino-7*H*-pyrrolo[2,3-d]pyrimidin-7-yl)-3-hydroxymethyl-1-methyl-4-methylenecyclopentane-1,2-diol (2-5)

Step A: (±)-(1 $\alpha$ ,2 $\alpha$ ,3 $\beta$ ,5 $\beta$ )-3-(Benzylloxymethyl)-5-(4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-(p-anisyldiphenylmethoxy)-4-methylenecyclopentanol (2-1)

Sodium hydride (3 eq) and 4-chloro-7H pyrrolo[2,3-d]pyrimidine (3 eq) are dissolved in anhydrous DMF and stirred at 120 °C for 15 min. A solution of 1-7 in anhydrous DMF is added and the reaction stirred overnight under argon atmosphere at 120 °C. The solvent is removed in vacuo and the residue taken up in dichloromethane. The organic layer is then washed with water and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After removing the solvent by evaporation under diminished pressure, the residue is purified by flash chromatography on silica gel to give the title compound 2-1.

Step B: (±)-(2 $\alpha$ ,3 $\beta$ ,5 $\beta$ )-3-(Benzylloxymethyl)-5-(4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-(p-anisyldiphenylmethoxy)-4-methylenecyclopentanone (2-2)

The product from Step A is processed according to the procedure detailed in Step G of Example 1 to give the title compound.

Step C: (±)-(1 $\alpha$ OH,2 $\alpha$ ,3 $\beta$ ,5 $\beta$ )-3-(Benzylloxymethyl)-5-(4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-(p-anisyldiphenylmethoxy)-1-methyl-4-methylenecyclopentanol (2-3)

The product from Step B is processed according to the procedure detailed in Step H of Example 1 to give the title compound.

Step D: (±)-(1 $\alpha$ OH,2 $\alpha$ ,3 $\beta$ ,5 $\beta$ )-3-(Benzylloxymethyl)-5-(4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-1-methyl-4-methylenecyclopentane-1,2-diol

This compound is obtained from the product of Step C by utilizing a similar procedure described in Step I of Example 1 to give the title compound.

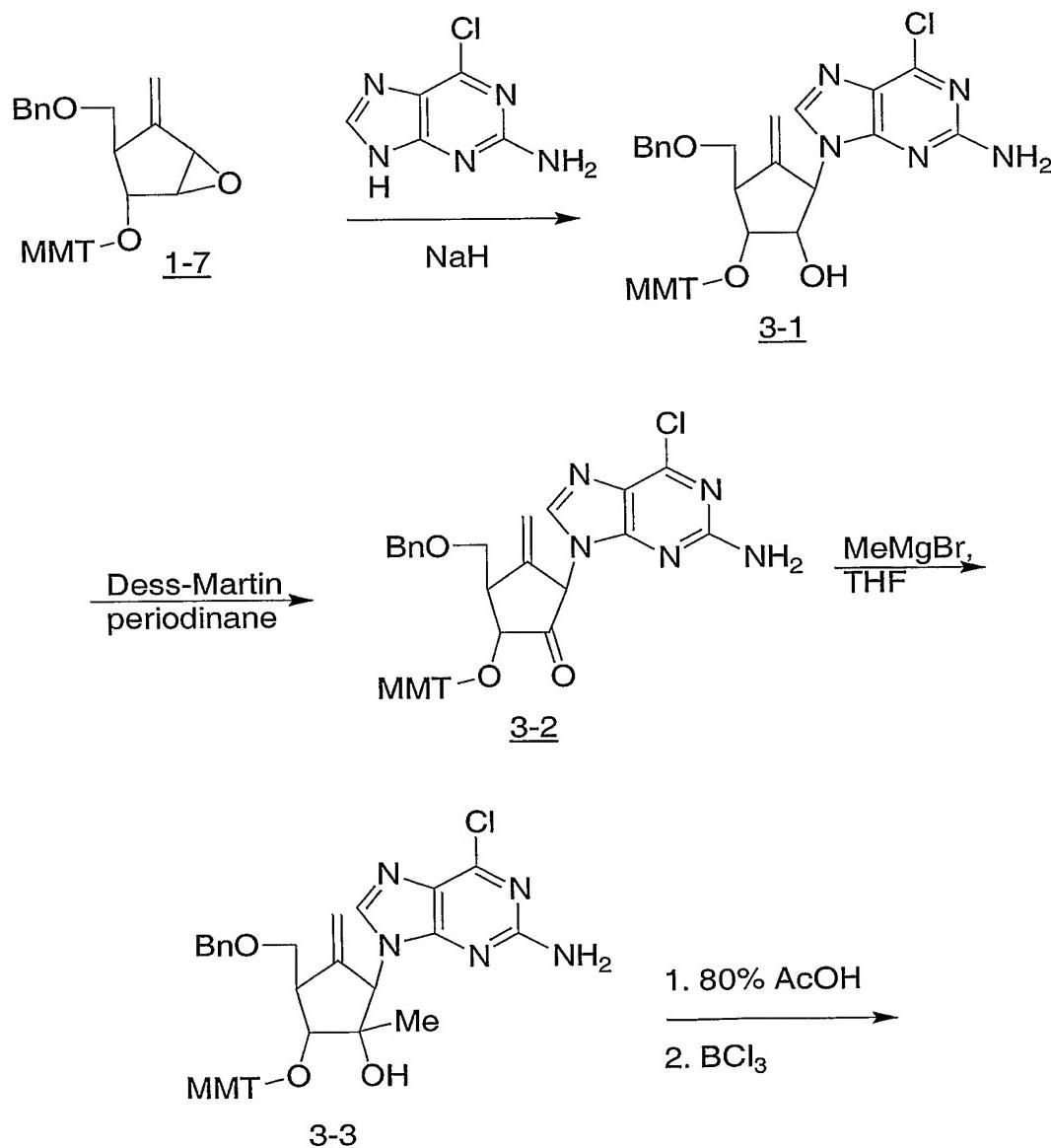
Step E: (±)-(1 $\alpha$ OH,2 $\alpha$ ,3 $\beta$ ,5 $\beta$ )-5-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-3-(hydroxymethyl)-1-methyl-4-methylenecyclopentane-1,2-diol (2-4)

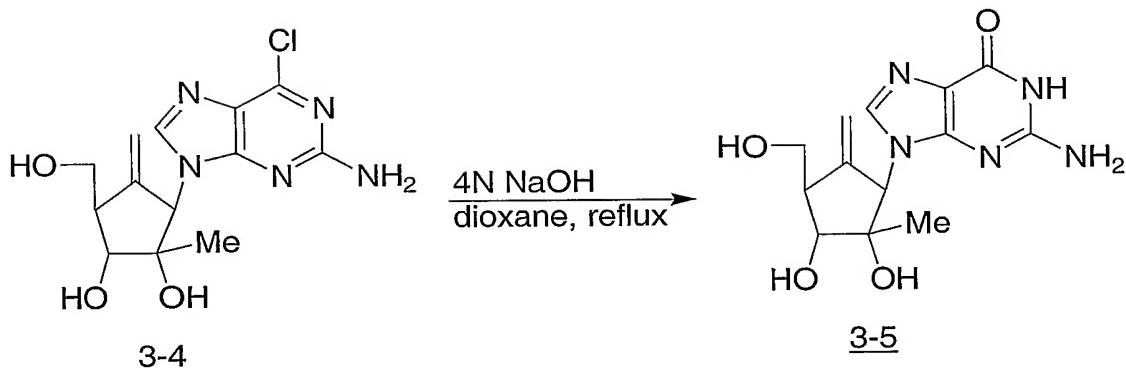
This compound is obtained from the product of Step D by utilizing a similar procedure described in Step J of Example 1.

Step F: ( $\pm$ )-(1 $\alpha$ OH,2 $\alpha$ ,3 $\beta$ ,5 $\beta$ )-5-(4-Amino-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-3-(hydroxymethyl)-1-methyl-4-methylenecyclopentane-1,2-diol (2-5)

The title compound is obtained by dissolving 2-4 in liquid ammonia and heating it at 100 °C in a steel bomb overnight. After evaporation, the remaining solid is washed with anhydrous THF. The solvent is then removed under reduced pressure and the residue purified by column chromatography.

Scheme 3



EXAMPLE 3

5       (±)-(1β,2αOH,3α,4β)-2-Amino-9-[2,3-dihydroxy-4-(hydroxymethyl)-2-methyl-5-  
methylene]cyclopentyl]-1,9-dihydro-6H-purin-6-one (3-5)

Step A:       (±)-(1α,2β,4β,5α)-2-(2-Amino-6-chloro-9H-purin-9-yl)-4-  
(benzyloxymethyl)-5-(p-anisylidiphenylmethoxy)-3-  
methylene]cyclopentanol (3-1)

10       Sodium hydride (67.2 mg of a 60% suspension, 1.68 mmol) and 2-amino-6-chloro-purine (285 mg, 1.68 mmol) were dissolved in anhydrous DMA (5 mL) and stirred at 120 °C for 15 min. A solution of compound 1-7 (280 mg, 0.56 mmol) in 1 mL DMA was added and the reaction was stirred overnight under argon at 120 °C. The solvent was removed by evaporation under diminished pressure and the residue was taken up in dichloromethane (20 mL). The organic layer was washed twice with water (15 mL) and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed by evaporation under diminished pressure and the residue purified by flash chromatography on silica gel (1:1 hexanes/EtOAc) to give 80 mg of the title compound 3-1 as a white foam.

20       Step B:       (±)-(2β,4β,5α)-2-(2-Amino-6-chloro-9H-purin-9-yl)-4-  
(benzyloxymethyl)-5-(p-anisylidiphenylmethoxy)-3-  
methylene]cyclopentanone (3-2)

25       Compound 3-2 is obtained by taking the compound from Step A in anhydrous dichloromethane and adding the solution to an ice-cold suspension of Dess-Martin periodinane (4 eq) in anhydrous dichloromethane under argon. After stirring the solution at room temperature for 4 d, the mixture is diluted with ethyl

acetate and poured into a solution of sodium thiosulfate in saturated sodium bicarbonate solution. The organic layer is separated and dried over anhydrous sodium sulfate. After evaporation, the residue is purified by flash chromatography on silica gel.

5

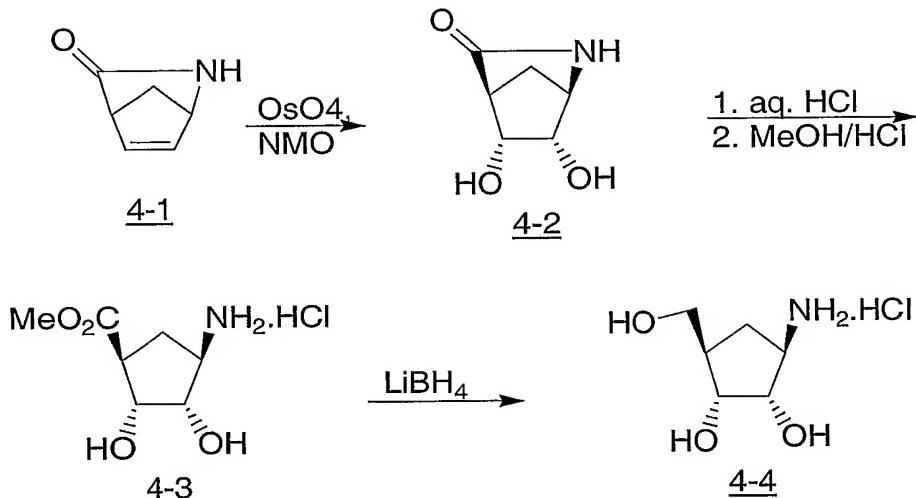
Step C: (±)-(1αOH,2β,4β,5α)-2-(2-Amino-6-chloro-9H-purin-9-yl)-4-(benzyloxymethyl)-5-(p-anisylidiphenylmethoxy)-1-methyl-3-methylenecyclopentanol (3-3)

Intermediate 3-2 is dissolved in anhydrous THF and then added to a  
10 solution of methylmagnesium bromide (4 eq) in anhydrous THF at -78 °C. The resulting mixture after stirring overnight at -70 °C to -50 °C is quenched with saturated NH<sub>4</sub>Cl solution. The resulting slurry is filtered through a celite pad. The residue on the pad is washed with ethyl acetate and the combined filtrate and washings transferred to a separatory funnel. The organic layer is washed with  
15 saturated aqueous NH<sub>4</sub>Cl solution, water, and brine. It is then dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated under diminished pressure. The residue is purified by flash chromatography to give the title compound 3-3.

20 Step D: (±)-(1αOH,2α,3β,5β)-5-(2-Amino-6-chloro-9H-purin-9-yl)-3-(benzyloxymethyl)-1-methyl-4-methylenecyclopentane-1,2-diol  
This compound is obtained from the product of Step C by utilizing a similar procedure described in Step I of Example 1 to give the title compound.

25 Step E: (±)-(1αOH,2α,3β,5β)-5-(2-Amino-6-chloro-9H-purin-9-yl)-3-(hydroxymethyl)-1-methyl-4-methylenecyclopentane-1,2-diol (3-4)  
This compound is obtained from the product of Step D by utilizing a similar procedure described in Step J of Example 1.

30 Step F: (±)-(1β,2αOH,3α,4β)-2-Amino-9-[2,3-dihydroxy-4-(hydroxymethyl)-2-methyl-5-methylenecyclopentyl]-1,9-dihydro-6H-purin-6-one (3-5)  
This compound is obtained from the product of Step E by utilizing a similar procedure described in Step K of Example 1.

Scheme 4Step A: (1R,4S,5R,6S)-5,6-Dihydroxy-2-azabicyclo[2.2.1]heptan-3-one (4-2)

To a mixture of (1R)-(-)-2-azabicyclo[2.2.1]hept-5-en-3-one (4-1) (10.9 g, 99.8 mmol) in dioxane was added 4-methylmorpholine-N-oxide (17.4 g, 148.52 mmol) and the reaction mixture was cooled in an ice-bath. To this solution was added osmium tetroxide (30 mL, 4% solution in water) and the mixture was stirred at room temperature for 3 h. Sodium bisulfite (17.0 g) was added and the residue was filtered through celite, concentrated in vacuo and passed through a short column of silica gel using CH<sub>2</sub>Cl<sub>2</sub>/MeOH (95:5) as eluent to afford the title compound as colorless solid; yield 7.5 g. The proton NMR spectral data in D<sub>2</sub>O were found to be identical to those given in *J.Org.Chem.* 46: 3268 (1981).

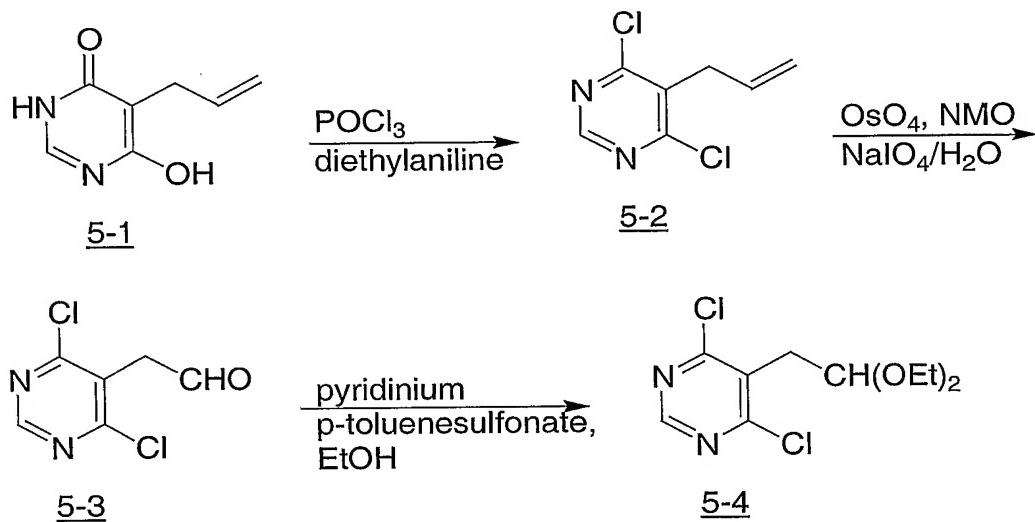
Step B: Methyl (1S,2R,3S,4R)-4-amino-2,3-dihydroxy-cyclopentanecarboxylate hydrochloride (4-3)

This compound was prepared following the procedure described by B. L. Kam and N. J. Oppenheimer in *J. Org. Chem.* 46: 3268 (1981) for the corresponding racemic compound.

Step C: (1R,2S,3R,5R)-3-Amino-5-(hydroxymethyl)cyclopentane-1,2-diol hydrochloride (4-4)

To a mixture of 4-3 (2.1 g, 9.9 mmol) in THF (10 mL) was added lithium borohydride (0.32 g, 14.6 mmol) under cooling to ice temperature and the

reaction mixture was stirred at room temperature overnight, evaporated in vacuo and treated with methanol. The mixture was cooled in an ice-bath and acidified with 0.1N HCl. The solvent was removed in vacuo and triturated with acetone. The residual oil was dried in vacuo and used without further purification as shown in Scheme 6 in the synthesis of 6-6.

Scheme 5Step A: 5-Allyl-4,6-dichloropyrimidine (5-2)

A mixture of 5-allyl-4,6-dihydroxypyrimidine (5-1) [prepared following the procedure described in *J. Med. Chem.*, 10: 665 (1967)] (6.0 g, 39.4 mmol), diethylaniline (7.5 mL, 46 mmol), benzyltriethylammonium chloride (18 g, 79 mmol) and  $\text{POCl}_3$  (20 mL) in acetonitrile (100 mL) was heated at 110 °C with stirring overnight. The reaction mixture was cooled and poured onto crushed ice, and extracted with ethyl acetate. The organic layer was washed with water (20 mL) dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated to an oil which was passed through a short band of silica gel using  $\text{CH}_2\text{Cl}_2$  as eluent; yield 3.3 g.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  3.67 (m, 2H,  $\text{CH}_2$ ), 5.14 (m, 2H,  $\text{CH}_2$ ), 5.89 (m, 1H,  $\text{CH}$ ), 8.66 (s, 1H, H-2).

20 Step B: (4,6-Dichloropyrimidine-5-yl)acetaldehyde (5-3)

This compound was prepared by modification of the procedure described in *J. Med. Chem.* 10: 665 (1967). A solution of 5-2 (3.0 g, 15.7 mmol) in dioxane (20 mL) was stirred with 4-methylmorpholine-N-oxide (2.8 g, 24 mmol) and osmium tetroxide (4% solution in water, 6.2 mL) for one h. Sodium bisulfite (2.6 g) was added to the mixture and the precipitated solid was removed by filtration through celite and the filtrate was concentrated in vacuo to a solid which was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (50 mL). Sodium periodate on silica gel (10% by weight, 50 g) was added to the solution. The reaction mixture was stirred at room temperature for 10 min. Silica gel was removed by filtration and the filtrate was washed with 5% aqueous sodium thiosulphate solution, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> and passed through a short column of silica gel using 0.5% methanol/CH<sub>2</sub>Cl<sub>2</sub> as eluent; yield 2.5 g.

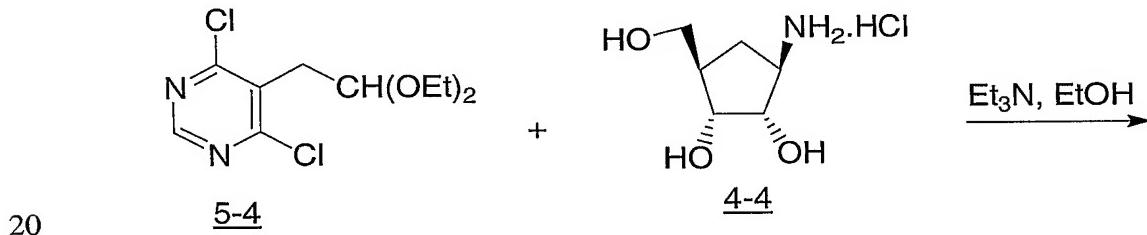
<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 4.14 (s, 1H, CH<sub>2</sub>), 8.73 (s, 1H, H-2), 9.80 (s, 1H, CHO).

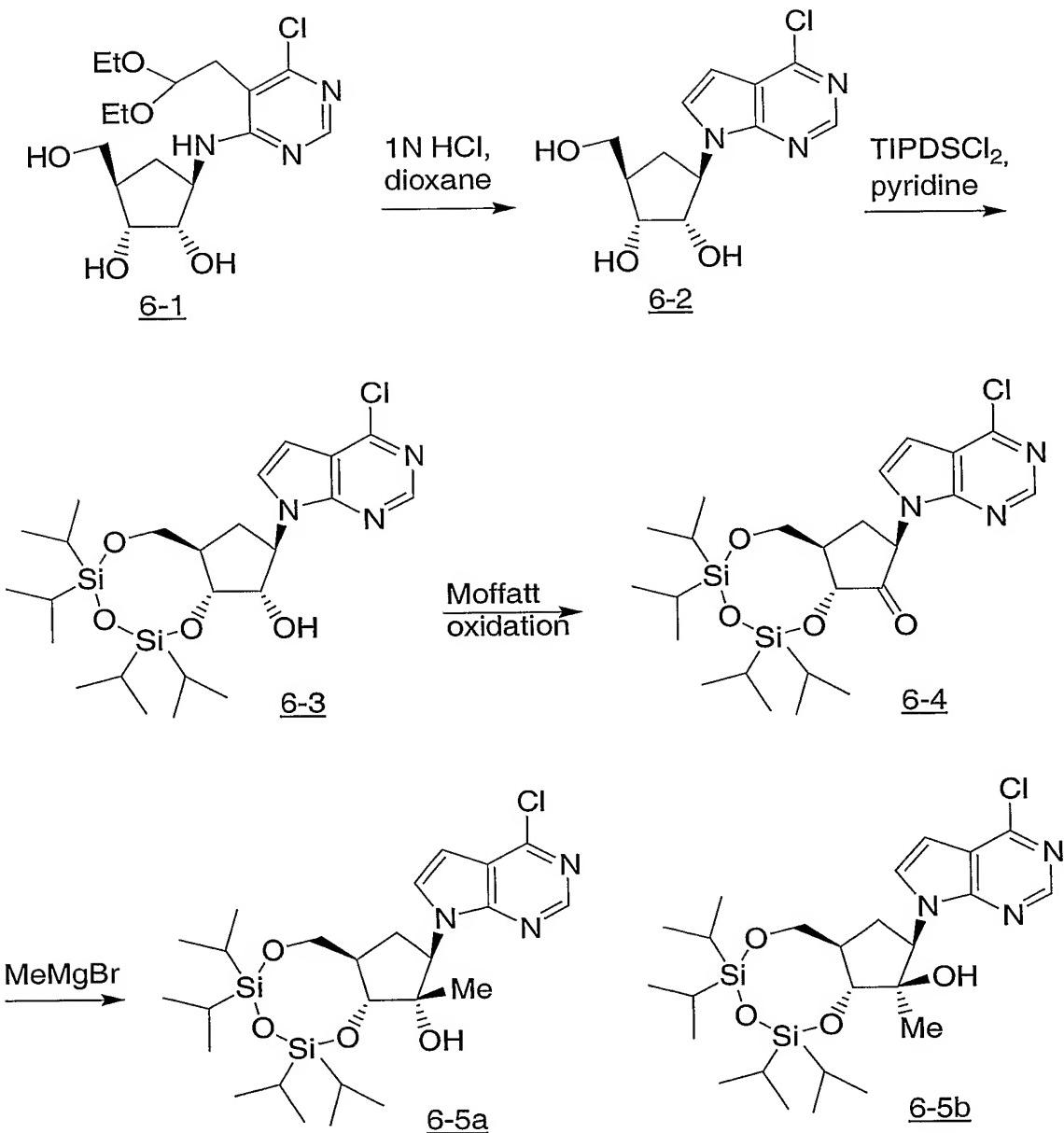
15 Step C: 4,6-Dichloro-5-(2,2-diethoxyethyl)pyrimidine (5-4)

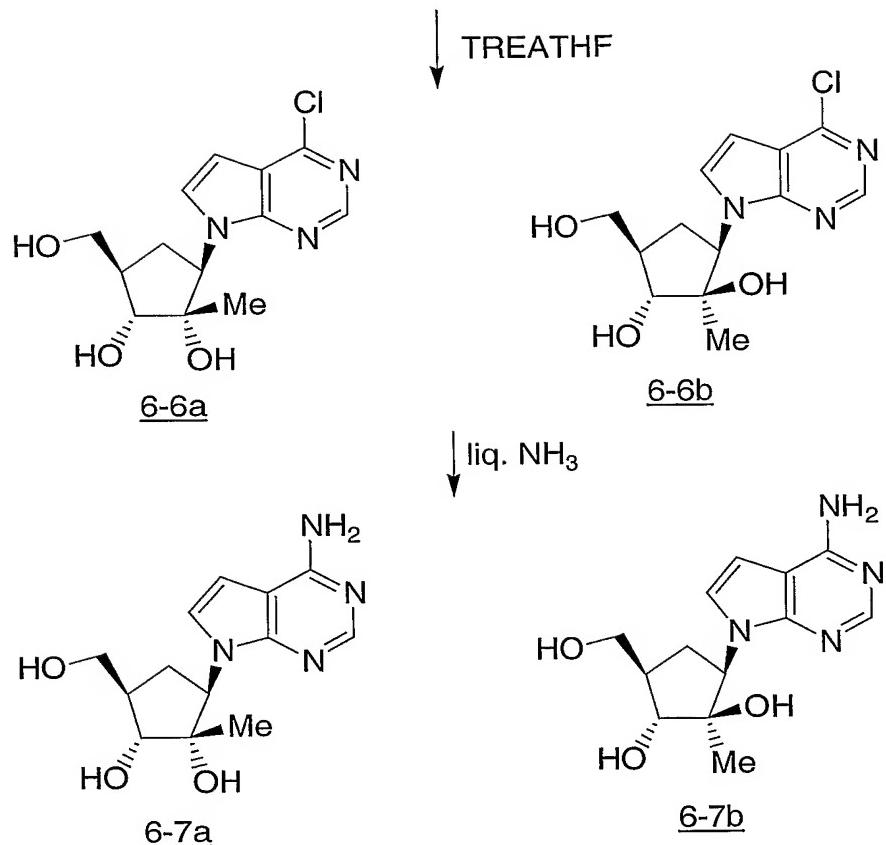
This compound was prepared from 5-3 following the procedure described in J. Med. Chem., 10: 665 (1967).

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.54 (2t, 6H, 2CH<sub>3</sub>), 3.27 (d, 2H, J=5.8Hz, CH<sub>2</sub>) , 3.59 and 3.73 (2m, 4H, 2 x OCH<sub>2</sub>), 4.82 (t, 1H, J=5.8 Hz and 11.4Hz, CH), 8.65 (s, 1H, H-2).

### Scheme 6





EXAMPLE 4

5

(1,2R,3R,5R)-5-(4-Amino-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-3-(hydroxymethyl)-1-methylcyclopentanediol-1,2-diol (6-7a)

(1,2R,3R,5R)-5-(4-Amino-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-3-(hydroxymethyl)-1-methylcyclopentanediol-1,2-diol (6-7b)

10

Step A: (1R,2S,3R,5R)-3-[{[6-chloro-5-(2,2-diethoxyethyl)pyrimidin-4-yl]amino}-5-(hydroxymethyl)cyclopentane-1,2-diol (6-1)

This compound was prepared from 5-4 and 4-4 following the procedure described in J. Med. Chem., 27: 534 (1984).

15

Step B: (1R,2S,3R,5R)-3-(4-Chloro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-5-(hydroxymethyl)cyclopentane-1,2-diol (6-2)

To a mixture of 6-1 (1.0 g, 2.6 mmol) in dioxane (15 mL) was added 1N HCl (4 mL) and the reaction mixture was stirred at room temperature for 24 h. The mixture was then cooled in an ice-bath and neutralized with ammonium hydroxide solution, and concentrated in vacuo. The residue was treated with EtOH and precipitated salts were removed by filtration. The filtrate was evaporated and the residue was purified by flash chromatography over silica gel using 10% MeOH/CH<sub>2</sub>Cl<sub>2</sub> as eluent to furnish the title compound 6-2 as a colorless oil; yield 0.42 g. The proton NMR spectrum was identical to the one reported in *J. Med. Chem.* 27: 534 (1984).

10

Step C: (6aR,8R,9S,9aR)-8-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2,2,4,4-tetraisopropylhexahydrocyclopenta[f][1,3,5,2,4]trioxadisilocin-9-ol (6-3)

A mixture of 6-2 (0.4 g, 1.4 mmol), TIPDS-dichloride (0.52 mL) and pyridine was stirred at room temperature for 1.5 h, diluted with water and extracted with ethyl acetate (2 x 50 mL). The organic layer was washed with water and dried over Na<sub>2</sub>SO<sub>4</sub>. The crude product (0.68 g) after evaporation was purified by column chromatography over silica gel using 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub> as eluent to furnish the title compound 6-3 as a colorless foam; yield 513 mg.

15 <sup>20</sup> <sup>25</sup> <sup>30</sup> <sup>35</sup> <sup>40</sup> <sup>45</sup> <sup>50</sup> <sup>55</sup> <sup>60</sup> <sup>65</sup> <sup>70</sup> <sup>75</sup> <sup>80</sup> <sup>85</sup> <sup>90</sup> <sup>95</sup> <sup>100</sup> <sup>105</sup> <sup>110</sup> <sup>115</sup> <sup>120</sup> <sup>125</sup> <sup>130</sup> <sup>135</sup> <sup>140</sup> <sup>145</sup> <sup>150</sup> <sup>155</sup> <sup>160</sup> <sup>165</sup> <sup>170</sup> <sup>175</sup> <sup>180</sup> <sup>185</sup> <sup>190</sup> <sup>195</sup> <sup>200</sup> <sup>205</sup> <sup>210</sup> <sup>215</sup> <sup>220</sup> <sup>225</sup> <sup>230</sup> <sup>235</sup> <sup>240</sup> <sup>245</sup> <sup>250</sup> <sup>255</sup> <sup>260</sup> <sup>265</sup> <sup>270</sup> <sup>275</sup> <sup>280</sup> <sup>285</sup> <sup>290</sup> <sup>295</sup> <sup>300</sup> <sup>305</sup> <sup>310</sup> <sup>315</sup> <sup>320</sup> <sup>325</sup> <sup>330</sup> <sup>335</sup> <sup>340</sup> <sup>345</sup> <sup>350</sup> <sup>355</sup> <sup>360</sup> <sup>365</sup> <sup>370</sup> <sup>375</sup> <sup>380</sup> <sup>385</sup> <sup>390</sup> <sup>395</sup> <sup>400</sup> <sup>405</sup> <sup>410</sup> <sup>415</sup> <sup>420</sup> <sup>425</sup> <sup>430</sup> <sup>435</sup> <sup>440</sup> <sup>445</sup> <sup>450</sup> <sup>455</sup> <sup>460</sup> <sup>465</sup> <sup>470</sup> <sup>475</sup> <sup>480</sup> <sup>485</sup> <sup>490</sup> <sup>495</sup> <sup>500</sup> <sup>505</sup> <sup>510</sup> <sup>515</sup> <sup>520</sup> <sup>525</sup> <sup>530</sup> <sup>535</sup> <sup>540</sup> <sup>545</sup> <sup>550</sup> <sup>555</sup> <sup>560</sup> <sup>565</sup> <sup>570</sup> <sup>575</sup> <sup>580</sup> <sup>585</sup> <sup>590</sup> <sup>595</sup> <sup>600</sup> <sup>605</sup> <sup>610</sup> <sup>615</sup> <sup>620</sup> <sup>625</sup> <sup>630</sup> <sup>635</sup> <sup>640</sup> <sup>645</sup> <sup>650</sup> <sup>655</sup> <sup>660</sup> <sup>665</sup> <sup>670</sup> <sup>675</sup> <sup>680</sup> <sup>685</sup> <sup>690</sup> <sup>695</sup> <sup>700</sup> <sup>705</sup> <sup>710</sup> <sup>715</sup> <sup>720</sup> <sup>725</sup> <sup>730</sup> <sup>735</sup> <sup>740</sup> <sup>745</sup> <sup>750</sup> <sup>755</sup> <sup>760</sup> <sup>765</sup> <sup>770</sup> <sup>775</sup> <sup>780</sup> <sup>785</sup> <sup>790</sup> <sup>795</sup> <sup>800</sup> <sup>805</sup> <sup>810</sup> <sup>815</sup> <sup>820</sup> <sup>825</sup> <sup>830</sup> <sup>835</sup> <sup>840</sup> <sup>845</sup> <sup>850</sup> <sup>855</sup> <sup>860</sup> <sup>865</sup> <sup>870</sup> <sup>875</sup> <sup>880</sup> <sup>885</sup> <sup>890</sup> <sup>895</sup> <sup>900</sup> <sup>905</sup> <sup>910</sup> <sup>915</sup> <sup>920</sup> <sup>925</sup> <sup>930</sup> <sup>935</sup> <sup>940</sup> <sup>945</sup> <sup>950</sup> <sup>955</sup> <sup>960</sup> <sup>965</sup> <sup>970</sup> <sup>975</sup> <sup>980</sup> <sup>985</sup> <sup>990</sup> <sup>995</sup> <sup>1000</sup> <sup>1005</sup> <sup>1010</sup> <sup>1015</sup> <sup>1020</sup> <sup>1025</sup> <sup>1030</sup> <sup>1035</sup> <sup>1040</sup> <sup>1045</sup> <sup>1050</sup> <sup>1055</sup> <sup>1060</sup> <sup>1065</sup> <sup>1070</sup> <sup>1075</sup> <sup>1080</sup> <sup>1085</sup> <sup>1090</sup> <sup>1095</sup> <sup>1100</sup> <sup>1105</sup> <sup>1110</sup> <sup>1115</sup> <sup>1120</sup> <sup>1125</sup> <sup>1130</sup> <sup>1135</sup> <sup>1140</sup> <sup>1145</sup> <sup>1150</sup> <sup>1155</sup> <sup>1160</sup> <sup>1165</sup> <sup>1170</sup> <sup>1175</sup> <sup>1180</sup> <sup>1185</sup> <sup>1190</sup> <sup>1195</sup> <sup>1200</sup> <sup>1205</sup> <sup>1210</sup> <sup>1215</sup> <sup>1220</sup> <sup>1225</sup> <sup>1230</sup> <sup>1235</sup> <sup>1240</sup> <sup>1245</sup> <sup>1250</sup> <sup>1255</sup> <sup>1260</sup> <sup>1265</sup> <sup>1270</sup> <sup>1275</sup> <sup>1280</sup> <sup>1285</sup> <sup>1290</sup> <sup>1295</sup> <sup>1300</sup> <sup>1305</sup> <sup>1310</sup> <sup>1315</sup> <sup>1320</sup> <sup>1325</sup> <sup>1330</sup> <sup>1335</sup> <sup>1340</sup> <sup>1345</sup> <sup>1350</sup> <sup>1355</sup> <sup>1360</sup> <sup>1365</sup> <sup>1370</sup> <sup>1375</sup> <sup>1380</sup> <sup>1385</sup> <sup>1390</sup> <sup>1395</sup> <sup>1400</sup> <sup>1405</sup> <sup>1410</sup> <sup>1415</sup> <sup>1420</sup> <sup>1425</sup> <sup>1430</sup> <sup>1435</sup> <sup>1440</sup> <sup>1445</sup> <sup>1450</sup> <sup>1455</sup> <sup>1460</sup> <sup>1465</sup> <sup>1470</sup> <sup>1475</sup> <sup>1480</sup> <sup>1485</sup> <sup>1490</sup> <sup>1495</sup> <sup>1500</sup> <sup>1505</sup> <sup>1510</sup> <sup>1515</sup> <sup>1520</sup> <sup>1525</sup> <sup>1530</sup> <sup>1535</sup> <sup>1540</sup> <sup>1545</sup> <sup>1550</sup> <sup>1555</sup> <sup>1560</sup> <sup>1565</sup> <sup>1570</sup> <sup>1575</sup> <sup>1580</sup> <sup>1585</sup> <sup>1590</sup> <sup>1595</sup> <sup>1600</sup> <sup>1605</sup> <sup>1610</sup> <sup>1615</sup> <sup>1620</sup> <sup>1625</sup> <sup>1630</sup> <sup>1635</sup> <sup>1640</sup> <sup>1645</sup> <sup>1650</sup> <sup>1655</sup> <sup>1660</sup> <sup>1665</sup> <sup>1670</sup> <sup>1675</sup> <sup>1680</sup> <sup>1685</sup> <sup>1690</sup> <sup>1695</sup> <sup>1700</sup> <sup>1705</sup> <sup>1710</sup> <sup>1715</sup> <sup>1720</sup> <sup>1725</sup> <sup>1730</sup> <sup>1735</sup> <sup>1740</sup> <sup>1745</sup> <sup>1750</sup> <sup>1755</sup> <sup>1760</sup> <sup>1765</sup> <sup>1770</sup> <sup>1775</sup> <sup>1780</sup> <sup>1785</sup> <sup>1790</sup> <sup>1795</sup> <sup>1800</sup> <sup>1805</sup> <sup>1810</sup> <sup>1815</sup> <sup>1820</sup> <sup>1825</sup> <sup>1830</sup> <sup>1835</sup> <sup>1840</sup> <sup>1845</sup> <sup>1850</sup> <sup>1855</sup> <sup>1860</sup> <sup>1865</sup> <sup>1870</sup> <sup>1875</sup> <sup>1880</sup> <sup>1885</sup> <sup>1890</sup> <sup>1895</sup> <sup>1900</sup> <sup>1905</sup> <sup>1910</sup> <sup>1915</sup> <sup>1920</sup> <sup>1925</sup> <sup>1930</sup> <sup>1935</sup> <sup>1940</sup> <sup>1945</sup> <sup>1950</sup> <sup>1955</sup> <sup>1960</sup> <sup>1965</sup> <sup>1970</sup> <sup>1975</sup> <sup>1980</sup> <sup>1985</sup> <sup>1990</sup> <sup>1995</sup> <sup>2000</sup> <sup>2005</sup> <sup>2010</sup> <sup>2015</sup> <sup>2020</sup> <sup>2025</sup> <sup>2030</sup> <sup>2035</sup> <sup>2040</sup> <sup>2045</sup> <sup>2050</sup> <sup>2055</sup> <sup>2060</sup> <sup>2065</sup> <sup>2070</sup> <sup>2075</sup> <sup>2080</sup> <sup>2085</sup> <sup>2090</sup> <sup>2095</sup> <sup>2100</sup> <sup>2105</sup> <sup>2110</sup> <sup>2115</sup> <sup>2120</sup> <sup>2125</sup> <sup>2130</sup> <sup>2135</sup> <sup>2140</sup> <sup>2145</sup> <sup>2150</sup> <sup>2155</sup> <sup>2160</sup> <sup>2165</sup> <sup>2170</sup> <sup>2175</sup> <sup>2180</sup> <sup>2185</sup> <sup>2190</sup> <sup>2195</sup> <sup>2200</sup> <sup>2205</sup> <sup>2210</sup> <sup>2215</sup> <sup>2220</sup> <sup>2225</sup> <sup>2230</sup> <sup>2235</sup> <sup>2240</sup> <sup>2245</sup> <sup>2250</sup> <sup>2255</sup> <sup>2260</sup> <sup>2265</sup> <sup>2270</sup> <sup>2275</sup> <sup>2280</sup> <sup>2285</sup> <sup>2290</sup> <sup>2295</sup> <sup>2300</sup> <sup>2305</sup> <sup>2310</sup> <sup>2315</sup> <sup>2320</sup> <sup>2325</sup> <sup>2330</sup> <sup>2335</sup> <sup>2340</sup> <sup>2345</sup> <sup>2350</sup> <sup>2355</sup> <sup>2360</sup> <sup>2365</sup> <sup>2370</sup> <sup>2375</sup> <sup>2380</sup> <sup>2385</sup> <sup>2390</sup> <sup>2395</sup> <sup>2400</sup> <sup>2405</sup> <sup>2410</sup> <sup>2415</sup> <sup>2420</sup> <sup>2425</sup> <sup>2430</sup> <sup>2435</sup> <sup>2440</sup> <sup>2445</sup> <sup>2450</sup> <sup>2455</sup> <sup>2460</sup> <sup>2465</sup> <sup>2470</sup> <sup>2475</sup> <sup>2480</sup> <sup>2485</sup> <sup>2490</sup> <sup>2495</sup> <sup>2500</sup> <sup>2505</sup> <sup>2510</sup> <sup>2515</sup> <sup>2520</sup> <sup>2525</sup> <sup>2530</sup> <sup>2535</sup> <sup>2540</sup> <sup>2545</sup> <sup>2550</sup> <sup>2555</sup> <sup>2560</sup> <sup>2565</sup> <sup>2570</sup> <sup>2575</sup> <sup>2580</sup> <sup>2585</sup> <sup>2590</sup> <sup>2595</sup> <sup>2600</sup> <sup>2605</sup> <sup>2610</sup> <sup>2615</sup> <sup>2620</sup> <sup>2625</sup> <sup>2630</sup> <sup>2635</sup> <sup>2640</sup> <sup>2645</sup> <sup>2650</sup> <sup>2655</sup> <sup>2660</sup> <sup>2665</sup> <sup>2670</sup> <sup>2675</sup> <sup>2680</sup> <sup>2685</sup> <sup>2690</sup> <sup>2695</sup> <sup>2700</sup> <sup>2705</sup> <sup>2710</sup> <sup>2715</sup> <sup>2720</sup> <sup>2725</sup> <sup>2730</sup> <sup>2735</sup> <sup>2740</sup> <sup>2745</sup> <sup>2750</sup> <sup>2755</sup> <sup>2760</sup> <sup>2765</sup> <sup>2770</sup> <sup>2775</sup> <sup>2780</sup> <sup>2785</sup> <sup>2790</sup> <sup>2795</sup> <sup>2800</sup> <sup>2805</sup> <sup>2810</sup> <sup>2815</sup> <sup>2820</sup> <sup>2825</sup> <sup>2830</sup> <sup>2835</sup> <sup>2840</sup> <sup>2845</sup> <sup>2850</sup> <sup>2855</sup> <sup>2860</sup> <sup>2865</sup> <sup>2870</sup> <sup>2875</sup> <sup>2880</sup> <sup>2885</sup> <sup>2890</sup> <sup>2895</sup> <sup>2900</sup> <sup>2905</sup> <sup>2910</sup> <sup>2915</sup> <sup>2920</sup> <sup>2925</sup> <sup>2930</sup> <sup>2935</sup> <sup>2940</sup> <sup>2945</sup> <sup>2950</sup> <sup>2955</sup> <sup>2960</sup> <sup>2965</sup> <sup>2970</sup> <sup>2975</sup> <sup>2980</sup> <sup>2985</sup> <sup>2990</sup> <sup>2995</sup> <sup>3000</sup> <sup>3005</sup> <sup>3010</sup> <sup>3015</sup> <sup>3020</sup> <sup>3025</sup> <sup>3030</sup> <sup>3035</sup> <sup>3040</sup> <sup>3045</sup> <sup>3050</sup> <sup>3055</sup> <sup>3060</sup> <sup>3065</sup> <sup>3070</sup> <sup>3075</sup> <sup>3080</sup> <sup>3085</sup> <sup>3090</sup> <sup>3095</sup> <sup>3100</sup> <sup>3105</sup> <sup>3110</sup> <sup>3115</sup> <sup>3120</sup> <sup>3125</sup> <sup>3130</sup> <sup>3135</sup> <sup>3140</sup> <sup>3145</sup> <sup>3150</sup> <sup>3155</sup> <sup>3160</sup> <sup>3165</sup> <sup>3170</sup> <sup>3175</sup> <sup>3180</sup> <sup>3185</sup> <sup>3190</sup> <sup>3195</sup> <sup>3200</sup> <sup>3205</sup> <sup>3210</sup> <sup>3215</sup> <sup>3220</sup> <sup>3225</sup> <sup>3230</sup> <sup>3235</sup> <sup>3240</sup> <sup>3245</sup> <sup>3250</sup> <sup>3255</sup> <sup>3260</sup> <sup>3265</sup> <sup>3270</sup> <sup>3275</sup> <sup>3280</sup> <sup>3285</sup> <sup>3290</sup> <sup>3295</sup> <sup>3300</sup> <sup>3305</sup> <sup>3310</sup> <sup>3315</sup> <sup>3320</sup> <sup>3325</sup> <sup>3330</sup> <sup>3335</sup> <sup>3340</sup> <sup>3345</sup> <sup>3350</sup> <sup>3355</sup> <sup>3360</sup> <sup>3365</sup> <sup>3370</sup> <sup>3375</sup> <sup>3380</sup> <sup>3385</sup> <sup>3390</sup> <sup>3395</sup> <sup>3400</sup> <sup>3405</sup> <sup>3410</sup> <sup>3415</sup> <sup>3420</sup> <sup>3425</sup> <sup>3430</sup> <sup>3435</sup> <sup>3440</sup> <sup>3445</sup> <sup>3450</sup> <sup>3455</sup> <sup>3460</sup> <sup>3465</sup> <sup>3470</sup> <sup>3475</sup> <sup>3480</sup> <sup>3485</sup> <sup>3490</sup> <sup>3495</sup> <sup>3500</sup> <sup>3505</sup> <sup>3510</sup> <sup>3515</sup> <sup>3520</sup> <sup>3525</sup> <sup>3530</sup> <sup>3535</sup> <sup>3540</sup> <sup>3545</sup> <sup>3550</sup> <sup>3555</sup> <sup>3560</sup> <sup>3565</sup> <sup>3570</sup> <sup>3575</sup> <sup>3580</sup> <sup>3585</sup> <sup>3590</sup> <sup>3595</sup> <sup>3600</sup> <sup>3605</sup> <sup>3610</sup> <sup>3615</sup> <sup>3620</sup> <sup>3625</sup> <sup>3630</sup> <sup>3635</sup> <sup>3640</sup> <sup>3645</sup> <sup>3650</sup> <sup>3655</sup> <sup>3660</sup> <sup>3665</sup> <sup>3670</sup> <sup>3675</sup> <sup>3680</sup> <sup>3685</sup> <sup>3690</sup> <sup>3695</sup> <sup>3700</sup> <sup>3705</sup> <sup>3710</sup> <sup>3715</sup> <sup>3720</sup> <sup>3725</sup> <sup>3730</sup> <sup>3735</sup> <sup>3740</sup> <sup>3745</sup> <sup>3750</sup> <sup>3755</sup> <sup>3760</sup> <sup>3765</sup> <sup>3770</sup> <sup>3775</sup> <sup>3780</sup> <sup>3785</sup> <sup>3790</sup> <sup>3795</sup> <sup>3800</sup> <sup>3805</sup> <sup>3810</sup> <sup>3815</sup> <sup>3820</sup> <sup>3825</sup> <sup>3830</sup> <sup>3835</sup> <sup>3840</sup> <sup>3845</sup> <sup>3850</sup> <sup>3855</sup> <sup>3860</sup> <sup>3865</sup> <sup>3870</sup> <sup>3875</sup> <sup>3880</sup> <sup>3885</sup> <sup>3890</sup> <sup>3895</sup> <sup>3900</sup> <sup>3905</sup> <sup>3910</sup> <sup>3915</sup> <sup>3920</sup> <sup>3925</sup> <sup>3930</sup> <sup>3935</sup> <sup>3940</sup> <sup>3945</sup> <sup>3950</sup> <sup>3955</sup> <sup>3960</sup> <sup>3965</sup> <sup>3970</sup> <sup>3975</sup> <sup>3980</sup> <sup>3985</sup> <sup>3990</sup> <sup>3995</sup> <sup>4000</sup> <sup>4005</sup> <sup>4010</sup> <sup>4015</sup> <sup>4020</sup> <sup>4025</sup> <sup>4030</sup> <sup>4035</sup> <sup>4040</sup> <sup>4045</sup> <sup>4050</sup> <sup>4055</sup> <sup>4060</sup> <sup>4065</sup> <sup>4070</sup> <sup>4075</sup> <sup>4080</sup> <sup>4085</sup> <sup>4090</sup> <sup>4095</sup> <sup>4100</sup> <sup>4105</sup> <sup>4110</sup> <sup>4115</sup> <sup>4120</sup> <sup>4125</sup> <sup>4130</sup> <sup>4135</sup> <sup>4140</sup> <sup>4145</sup> <sup>4150</sup> <sup>4155</sup> <sup>4160</sup> <sup>4165</sup> <sup>4170</sup> <sup>4175</sup> <sup>4180</sup> <sup>4185</sup> <sup>4190</sup> <sup>4195</sup> <sup>4200</sup> <sup>4205</sup> <sup>4210</sup> <sup>4215</sup> <sup>4220</sup> <sup>4225</sup> <sup>4230</sup> <sup>4235</sup> <sup>4240</sup> <sup>4245</sup> <sup>4250</sup> <sup>4255</sup> <sup>4260</sup> <sup>4265</sup> <sup>4270</sup> <sup>4275</sup> <sup>4280</sup> <sup>4285</sup> <sup>4290</sup> <sup>4295</sup> <sup>4300</sup> <sup>4305</sup> <sup>4310</sup> <sup>4315</sup> <sup>4320</sup> <sup>4325</sup> <sup>4330</sup> <sup>4335</sup> <sup>4340</sup> <sup>4345</sup> <sup>4350</sup> <sup>4355</sup> <sup>4360</sup> <sup>4365</sup> <sup>4370</sup> <sup>4375</sup> <sup>4380</sup> <sup>4385</sup> <sup>4390</sup> <sup>4395</sup> <sup>4400</sup> <sup>4405</sup> <sup>4410</sup> <sup>4415</sup> <sup>4420</sup> <sup>4425</sup> <sup>4430</sup> <sup>4435</sup> <sup>4440</sup> <sup>4445</sup> <sup>4450</sup> <sup>4455</sup> <sup>4460</sup> <sup>4465</sup> <sup>4470</sup> <sup>4475</sup> <sup>4480</sup> <sup>4485</sup> <sup>4490</sup> <sup>4495</sup> <sup>4500</sup> <sup>4505</sup> <sup>4510</sup> <sup>4515</sup> <sup>4520</sup> <sup>4525</sup> <sup>4530</sup> <sup>4535</sup> <sup>4540</sup> <sup>4545</sup> <sup>4550</sup> <sup>4555</sup> <sup>4560</sup> <sup>4565</sup> <sup>4570</sup> <sup>4575</sup> <sup>4580</sup> <sup>4585</sup> <sup>4590</sup> <sup>4595</sup> <sup>4600</sup> <sup>4605</sup> <sup>4610</sup> <sup>4615</sup> <sup>4620</sup> <sup>4625</sup> <sup>4630</sup> <sup>4635</sup> <sup>4640</sup> <sup>4645</sup> <sup>4650</sup> <sup>4655</sup> <sup>4660</sup> <sup>4665</sup> <sup>4670</sup> <sup>4675</sup> <sup>4680</sup> <sup>4685</sup> <sup>4690</sup> <sup>4695</sup> <sup>4700</sup> <sup>4705</sup> <sup>4710</sup> <sup>4715</sup> <sup>4720</sup> <sup>4725</sup> <sup>4730</sup> <sup>4735</sup> <sup>4740</sup> <sup>4745</sup> <sup>4750</sup> <sup>4755</sup> <sup>4760</sup> <sup>4765</sup> <sup>4770</sup> <sup>4775</sup> <sup>4780</sup> <sup>4785</sup> <sup>4790</sup> <sup>4795</sup> <sup>4800</sup> <sup>4805</sup> <sup>4810</sup> <sup>4815</sup> <sup>4820</sup> <sup>4825</sup> <sup>4830</sup> <sup>4835</sup> <sup>4840</sup> <sup>4845</sup> <sup>4850</sup> <sup>4855</sup> <sup>4860</sup> <sup>4865</sup> <sup>4870</sup> <sup>4875</sup> <sup>4880</sup> <sup>4885</sup> <sup>4890</sup> <sup>4895</sup> <sup>4900</sup> <sup>4905</sup> <sup>4910</sup> <sup>4915</sup> <sup>4920</sup> <sup>4925</sup> <sup>4930</sup> <sup>4935</sup> <sup>4940</sup> <sup>4945</sup> <sup>4950</sup> <sup>4955</sup> <sup>4960</sup> <sup>4965</sup> <sup>4970</sup> <sup>4975</sup> <sup>4980</sup> <sup>4985</sup> <sup>4990</sup> <sup>4995</sup> <sup>5000</sup> <sup>5005</sup> <sup>5010</sup> <sup>5015</sup> <sup>5020</sup> <sup>5025</sup> <sup>5030</sup> <sup>5035</sup> <sup>5040</sup> <sup>5045</sup> <sup>5050</sup> <sup>5055</sup> <sup>5060</sup> <sup>5065</sup> <sup>5070</sup> <sup>5075</sup> <sup>5080</sup> <sup>5085</sup> <sup>5090</sup> <sup>5095</sup> <sup>5100</sup> <sup>5105</sup> <sup>5110</sup> <sup>5115</sup> <sup>5120</sup> <sup>5125</sup> <sup>5130</sup> <sup>5135</sup> <sup>5140</sup> <sup>5145</sup> <sup>5150</sup> <sup>5155</sup> <sup>5160</sup> <sup>5165</sup> <sup>5170</sup> <sup>5175</sup> <sup>5180</sup> <sup>5185</sup> <sup>5190</sup> <sup>5195</sup> <sup>5200</sup> <sup>5205</sup> <sup>5210</sup> <sup>5215</sup> <sup>5220</sup> <sup>5225</sup> <sup>5230</sup> <sup>5235</sup> <sup>5240</sup> <sup>5245</sup> <sup>5250</sup> <sup>5255</sup> <sup>5260</sup> <sup>5265</sup> <sup>5270</sup> <sup>5275</sup> <sup>5280</sup> <sup>5285</sup> <sup>5290</sup> <sup>5295</sup> <sup>5300</sup> <sup>5305</sup> <sup>5310</sup> <sup>5315</sup> <sup>5320</sup> <sup>5325</sup> <sup>5330</sup> <sup>5335</sup> <sup>5340</sup> <sup>5345</sup> <sup>5350</sup> <sup>5355</sup> <sup>5360</sup> <sup>5365</sup> <sup>5370</sup> <sup>5375</sup> <sup>5380</sup> <sup>5385</sup> <sup>5390</sup> <sup>5395</sup> <sup>5400</sup> <sup>5405</sup> <sup>5410</sup> <sup>5415</sup> <sup>5420</sup> <sup>5425</sup> <sup>5430</sup> <sup>5435</sup> <sup>5440</sup> <sup>5445</sup> <sup>5450</sup> <sup>5455</sup</sup>

Step E: (6aR,8R,9S,9aR)-8-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2,2,4,4-tetraisopropyl-9-methylhexahydrocyclopenta-[f][1,3,5,2,4]trioxadisilocin-9-ol (6-5a) and

5 (6aR,8R,9R,9aR)-8-(4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2,2,4,4-tetraisopropyl-9-methylhexahydrocyclopenta-[f][1,3,5,2,4]trioxadisilocin-9-ol (6-5b)

To a cooled solution of 6-4 (0.4 g, 0.7 mmol) in toluene under argon cooled to -10 °C was added methylmagnesium bromide (3M soln. in ether, 0.5 mL, 1.4 mmol) and the reaction mixture was stirred at room temperature for 6 h. To this 10 solution was added an additional methylmagnesium bromide (0.25 mL, 0.7 mmol) and the reaction mixture was stirred overnight. It was then cooled to 0°C and poured into ice water and extracted with ethyl acetate (3 x 50 mL). The organic layer was washed with water (2 x 15 mL) and dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to an oil 15 (0.4 g) which was purified by column chromatography over silica gel using 1-5% dichloromethane-acetone as eluant to furnish α-methyl isomer 6-5b (90 mg) followed by the β-methyl isomer 6-5a (25 mg).

20 6-5b: <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.01–1.12 (m, 28H), 1.26 (s, 3H), 2.08–2.16 (m, 3H), 2.51 (s, 1H), 3.76–3.85 (m, 1H), 4.00–4.15 (m, 2H), 4.90–4.99 (m, 1H), 6.61 (d, 1H, J = 3.6 Hz), 7.46 (d, 1H, J = 3.6 Hz), 8.60 (s, 1H); ESMS (C<sub>25</sub>H<sub>42</sub>ClN<sub>3</sub>O<sub>4</sub>Si<sub>2</sub>, 540.24 M+1).

25 6-5a: <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 0.78 (s, 3H), 1.01–1.18 (m, 28H), 2.30–2.36 (m, 3H), 2.87 (s, 1H), 3.86–3.92 (m, 1H), 4.04–4.18 (m, 2H), 5.01–5.10 (m, 1H), 6.61 (d, 1H, J = 3.6 Hz), 7.28 (d, 1H, J = 3.6 Hz), 8.62 (s, 1H), ESMS (C<sub>25</sub>H<sub>42</sub>ClN<sub>3</sub>O<sub>4</sub>Si<sub>2</sub>, 540.24 M+1).

Step F: (1R,2R,3R,5R)-5-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-3-(hydroxymethyl)-1-methylcyclopentane-1,2-diol (6-6b)

30 To a solution of 6-5b (24 mg, 0.45 mmol) in anhydrous THF (1 mL) was added triethylamine (0.03 mL) and TREATHF (0.06 mL) and reaction mixture was stirred at room temperature overnight. It was concentrated in vacuo and co-evaporated with toluene and purified by column chromatography over silica gel using 10% MeOH in dichloromethane as eluent to furnish 6-6b (13 mg).

35 <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 0.99 (s, 3H), 1.89–2.05 (m, 2H), 2.04–2.11 (m, 1H), 3.44–3.52 (m, 2H), 3.55–3.60 (m, 1H), 4.75 (t, 1H), 4.81 (bs, 1H), 5.00–5.07 (m, 2H), 6.62

(d, 1H,  $J = 3.6$  Hz), 7.80 (d, 1H,  $J = 3.6$  Hz), 8.60 (s, 1H); ESMS ( $C_{13}H_{16}ClN_3O_3$ , 298.0 M+1).

5                   (1S,2R,3R,5R)-5-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-3-(hydroxymethyl)-1-methylcyclopentane-1,2-diol (6-6a)

Compound 6-5a (25 mg) was treated with TREATHF under identical experimental conditions as with 6-5b to furnish 6-6a in 60% yield.

<sup>1</sup>HNMR (DMSO-d<sub>6</sub>)  $\delta$  0.57 (s, 3H), 1.9-1.97 (m, 1H), 2.05-2.12 (m, 1H), 2.36-2.44 (m, 1H), 3.61-3.65 (m, 3H), 4.52 (bs, 1H), 4.73 (d, 1H,  $J = 6.8$  Hz), 4.80 (t, 1H), 5.03-

10       5.07 (m, 1H), 6.65 (d, 1H,  $J = 3.6$  Hz), 7.91 (d, 1H,  $J = 3.6$  Hz), 8.62 (s, 1H); ESMS ( $C_{13}H_{16}ClN_3O_3$ , 298.0 M+1).

Step G:           (1R,2R,3R,5R)-5-(4-Amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-3-(hydroxymethyl)-1-methylcyclopentane-1,2-diol (6-7b)

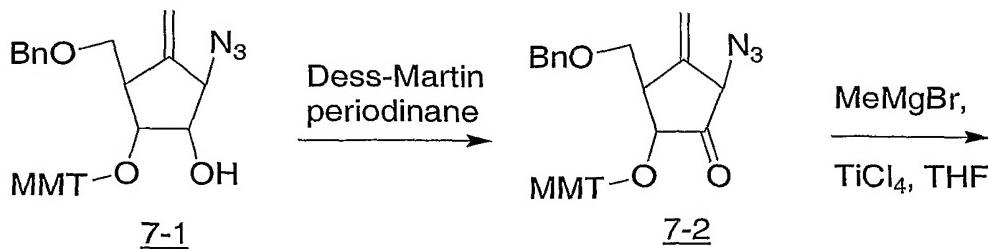
15       A mixture of 6-6b (2.0 mg) and liquid ammonia is heated in a steel bomb at 120 °C overnight. The residue was purified by reverse phase HPLC to afford 6-7b.

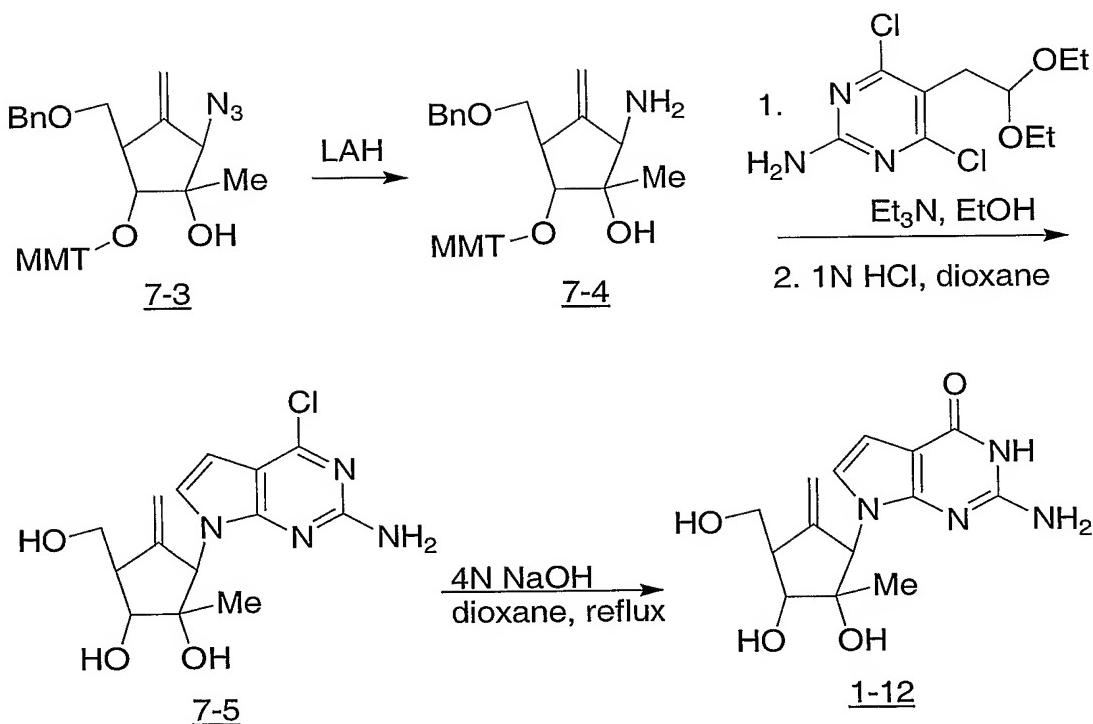
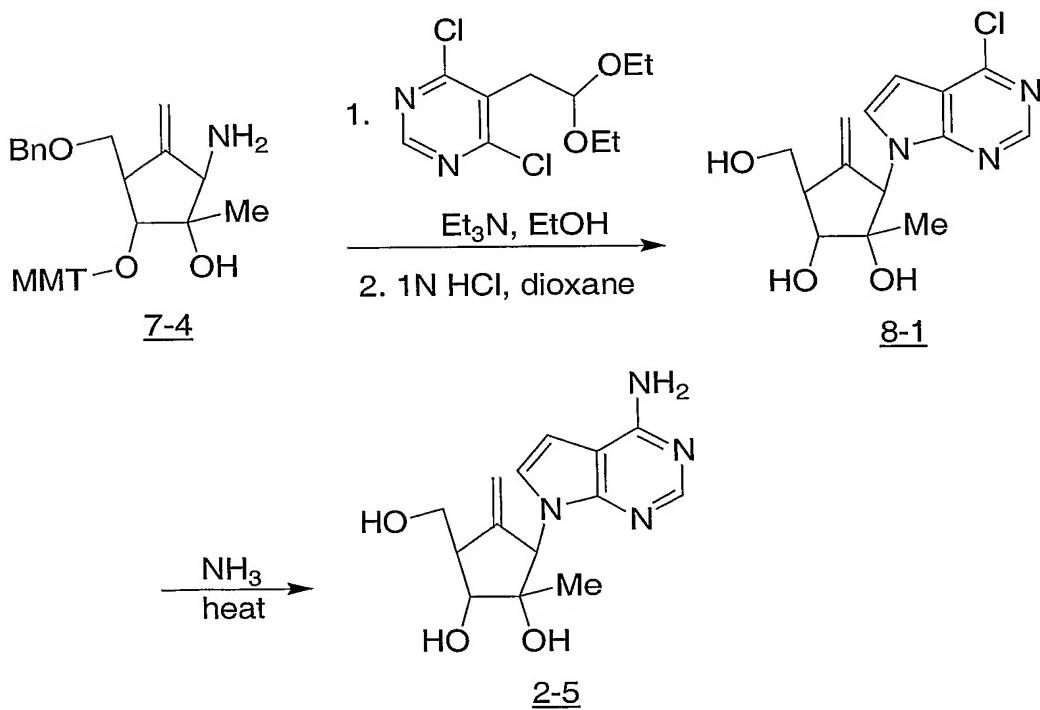
20                   (1S,2R,3R,5R)-5-(4-Amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-3-(hydroxymethyl)-1-methylcyclopentane-1,2-diol (6-7a)

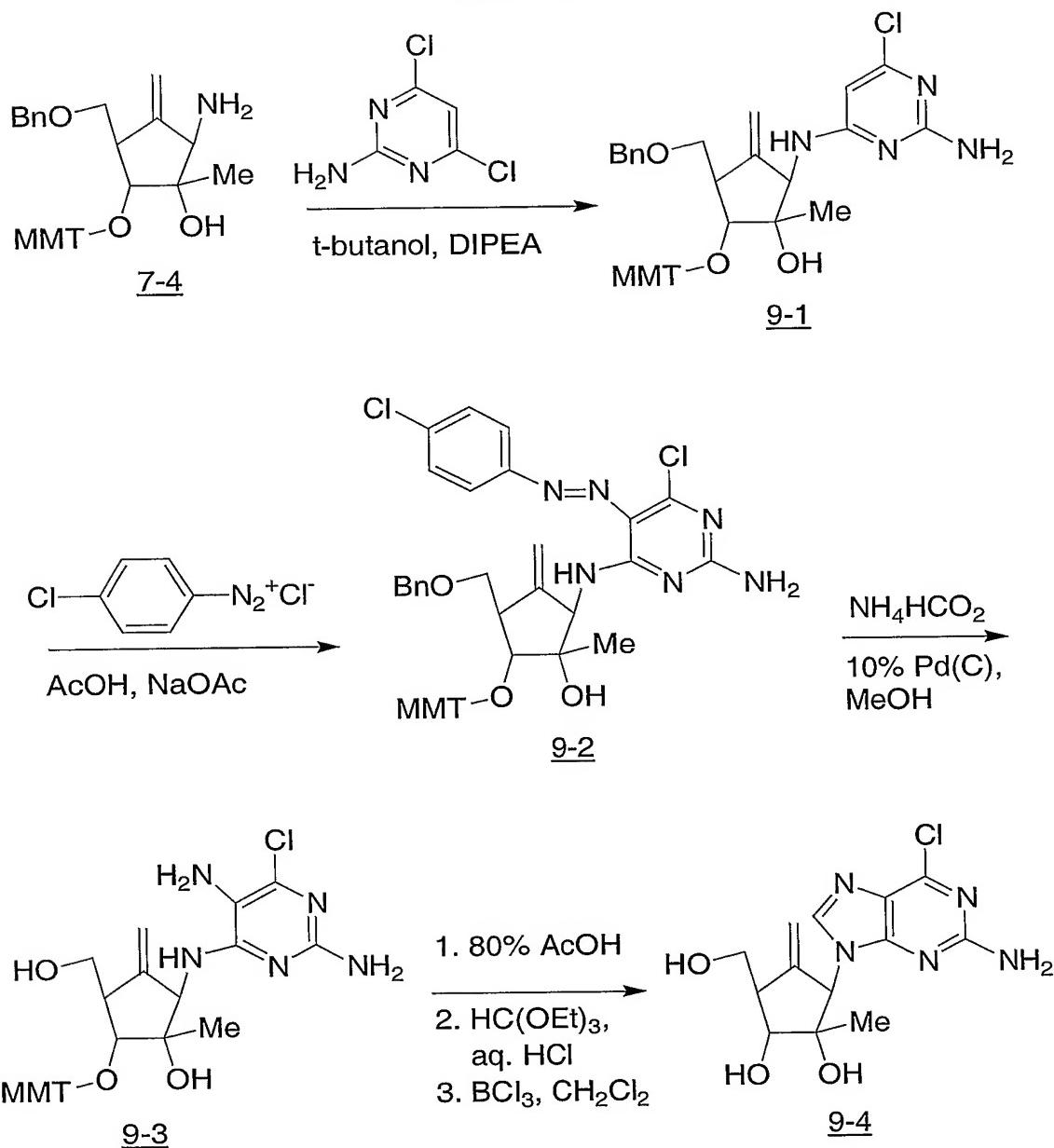
A mixture of 6-6a (2.0 mg) and liquid ammonia is heated in a steel bomb at 120 °C overnight. The residue was purified by reverse phase HPLC to afford 6-7a.

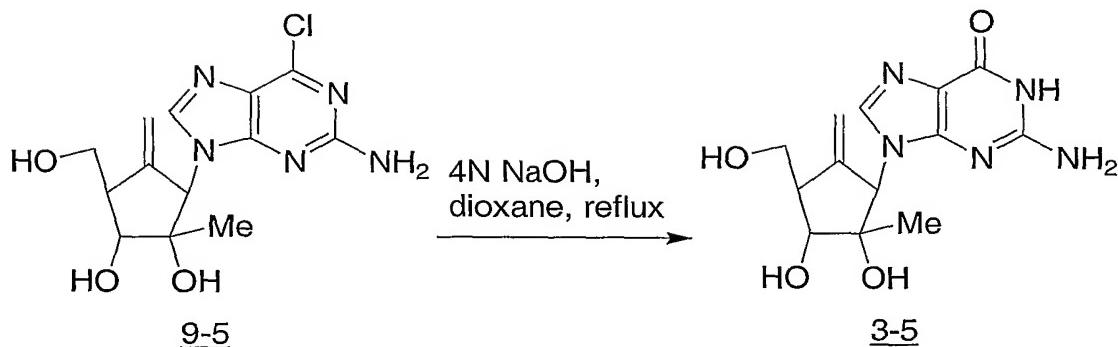
25       Examples 1, 2, and 3 can also prepared according to procedures depicted in Schemes 7, 8, and 9, respectively.

Scheme 7



Scheme 8

Scheme 9



### BIOLOGICAL ASSAYS

5           The assays employed to measure the inhibition of HCV NS5B polymerase and HCV replication are described below.

The effectiveness of the compounds of the present invention as inhibitors of HCV NS5B RNA-dependent RNA polymerase (RdRp) was measured in the following assay.

10    A. Assay for Inhibition of HCV NS5B Polymerase:

This assay was used to measure the ability of the carbocyclic nucleoside derivatives of the present invention to inhibit the enzymatic activity of the RNA-dependent RNA polymerase (NS5B) of the hepatitis C virus (HCV) on a heteromeric RNA template.

15

Procedure:

Assay Buffer Conditions: (50  $\mu\text{L}$  -total/reaction)

20 mM Tris, pH 7.5

50  $\mu\text{M}$  EDTA

20

5 mM DTT

2 mM MgCl<sub>2</sub>

80 mM KCl

0.4 U/ $\mu\text{L}$  RNasin (Promega, stock is 40 units/ $\mu\text{L}$ )

25

0.75  $\mu\text{g}$  t500 (a 500-nt RNA made using T7 runoff transcription with a sequence from the NS2/3 region of the hepatitis C genome)

1.6  $\mu\text{g}$  purified hepatitis C NS5B (form with 21 amino acids C-terminally truncated)

1 µM A,C,U,GTP (Nucleoside triphosphate mix)  
[alpha-<sup>32</sup>P]-GTP or [alpha-<sup>33</sup>P]-GTP

The compounds were tested at various concentrations up to 100 µM final concentration.

5 An appropriate volume of reaction buffer was made including enzyme and template t500. Carbocyclic nucleoside derivatives of the present invention were pipetted into the wells of a 96-well plate. A mixture of nucleoside triphosphates (NTP's), including the radiolabeled GTP, was made and pipetted into the wells of a 96-well plate. The reaction was initiated by addition of the enzyme-template reaction 10 solution and allowed to proceed at room temperature for 1-2 h.

The reaction was quenched by addition of 20 µL 0.5M EDTA, pH 8.0. Blank reactions in which the quench solution was added to the NTPs prior to the addition of the reaction buffer were included.

15 50 µL of the quenched reaction were spotted onto DE81 filter disks (Whatman) and allowed to dry for 30 min. The filters were washed with 0.3 M ammonium formate, pH 8 (150 mL/wash until the cpm in 1 mL wash is less than 100, usually 6 washes). The filters were counted in 5-mL scintillation fluid in a scintillation counter.

20 The percentage of inhibition was calculated according to the following equation: %Inhibition = [1-(cpm in test reaction - cpm in blank) / (cpm in control reaction - cpm in blank)] x 100.

Representative compounds tested in the HCV NS5B polymerase assay exhibited IC<sub>50</sub>'s less than 100 micromolar.

25 **B. Assay for Inhibition of HCV RNA Replication:**

The compounds of the present invention were also evaluated for their ability to affect the replication of Hepatitis C Virus RNA in cultured hepatoma (HuH-7) cells containing a subgenomic HCV Replicon. The details of the assay are described below. This Replicon assay is a modification of that described in V. 30 Lohmann, F. Korner, J-O. Koch, U. Herian, L. Theilmann, and R. Bartenschlager, "Replication of a Sub-genomic Hepatitis C Virus RNAs in a Hepatoma Cell Line," Science 285:110 (1999).

**Protocol:**

The assay was an *in situ* Ribonuclease protection, Scintillation Proximity based-plate assay (SPA). 10,000 - 40,000 cells were plated in 100-200  $\mu$ L of media containing 0.8mg/mL G418 in 96-well cytostar plates (Amersham). Compounds were added to cells at various concentrations up to 100  $\mu$ M in 1% DMSO  
5 at time 0 to 18 h and then cultured for 24-96 h. Cells were fixed (20 min, 10% formalin), permeabilized (20 min, 0.25% Triton X-100/PBS) and hybridized (overnight, 50°C) with a single-stranded  $^{33}$ P RNA probe complementary to the (+) strand NS5B (or other genes) contained in the RNA viral genome. Cells were washed, treated with RNase, washed, heated to 65°C and counted in a Top-Count.  
10 Inhibition of replication was read as a decrease in counts per minute (cpm).

Human HuH-7 hepatoma cells, which were selected to contain a subgenomic replicon, carry a cytoplasmic RNA consisting of an HCV 5' non-translated region (NTR), a neomycin selectable marker, an EMCV IRES (internal ribosome entry site), and HCV non-structural proteins NS3 through NS5B, followed  
15 by the 3' NTR.

Representative compounds tested in the replication assay exhibited EC<sub>50</sub>'s less than 100 micromolar.

The carbocyclic nucleoside derivatives of the present invention were  
20 also evaluated for cellular toxicity and anti-viral specificity in the counterscreens described below.

#### C. COUNTERSCREENS:

The ability of the carbocyclic nucleoside derivatives of the present invention to inhibit human DNA polymerases was measured in the following assays.  
25

##### a. Inhibition of Human DNA Polymerases alpha and beta:

###### Reaction Conditions:

30 50  $\mu$ L reaction volume

###### Reaction buffer components:

20 mM Tris-HCl, pH 7.5

200  $\mu$ g/mL bovine serum albumin

35 100 mM KCl

2 mM  $\beta$ -mercaptoethanol

10 mM MgCl<sub>2</sub>

1.6  $\mu$ M dA, dG, dC, dTTP

$\alpha$ -<sup>33</sup>P-dATP

5

Enzyme and template:

0.05 mg/mL gapped fish sperm DNA template

0.01 U/ $\mu$ L DNA polymerase  $\alpha$  or  $\beta$

10 Preparation of gapped fish sperm DNA template:

Add 5  $\mu$ L 1M MgCl<sub>2</sub> to 500  $\mu$ L activated fish sperm DNA (USB 70076);

Warm to 37°C and add 30  $\mu$ L of 65 U/ $\mu$ L of exonuclease III (GibcoBRL 18013-011);

Incubate 5 min at 37°C;

Terminate reaction by heating to 65 °C for 10 min;

15 Load 50-100  $\mu$ L aliquots onto Bio-spin 6 chromatography columns (Bio-Rad 732-

6002) equilibrated with 20 mM Tris-HCl, pH 7.5;

Elute by centrifugation at 1,000Xg for 4 min;

Pool eluate and measure absorbance at 260 nm to determine concentration.

20 The DNA template was diluted into an appropriate volume of 20 mM Tris-HCl, pH 7.5 and the enzyme was diluted into an appropriate volume of 20 mM Tris-HCl, containing 2 mM  $\beta$ -mercaptoethanol, and 100 mM KCl. Template and enzyme were pipetted into microcentrifuge tubes or a 96 well plate. Blank reactions excluding enzyme and control reactions excluding test compound were also prepared

25 using enzyme dilution buffer and test compound solvent, respectively. The reaction was initiated with reaction buffer with components as listed above. The reaction was incubated for 1 hour at 37°C. The reaction was quenched by the addition of 20  $\mu$ L 0.5M EDTA. 50  $\mu$ L of the quenched reaction was spotted onto Whatman DE81 filter disks and air dried. The filter disks were repeatedly washed with 150 mL 0.3M

30 ammonium formate, pH 8 until 1 mL of wash is < 100 cpm. The disks were washed twice with 150 mL absolute ethanol and once with 150 mL anhydrous ether, dried and counted in 5 mL scintillation fluid.

The percentage of inhibition was calculated according to the following equation: % inhibition = [1-(cpm in test reaction - cpm in blank)/(cpm in control reaction - cpm in blank)] x 100.

5    b. Inhibition of Human DNA Polymerase gamma :

The potential for inhibition of human DNA polymerase gamma was measured in reactions that included 0.5 ng/ µL enzyme; 10 µM dATP, dGTP, dCTP, and TTP; 2 µCi/reaction [ $\alpha$ -<sup>33</sup>P]-dATP, and 0.4 µg/µL activated fish sperm DNA (purchased from US Biochemical) in a buffer containing 20 mM Tris pH8, 2 mM  $\beta$ -mercaptoethanol, 50 mM KCl, 10 mM MgCl<sub>2</sub>, and 0.1 µg/µL BSA. Reactions were allowed to proceed for 1 h at 37°C and were quenched by addition of 0.5 M EDTA to a final concentration of 142 mM. Product formation was quantified by anion exchange filter binding and scintillation counting. Compounds were tested at up to 50 µM.

15       The percentage of inhibition was calculated according to the following equation: % inhibition = [1-(cpm in test reaction - cpm in blank)/(cpm in control reaction - cpm in blank)] x 100.

20       The ability of the carbocyclic nucleoside derivatives of the present invention to inhibit HIV infectivity and HIV spread was measured in the following assays.

c.       HIV Infectivity Assay

Assays were performed with a variant of HeLa Magi cells expressing both CXCR4 and CCR5 selected for low background  $\beta$ -galactosidase ( $\beta$ -gal) expression. Cells were infected for 48 h, and  $\beta$ -gal production from the integrated HIV-1 LTR promoter was quantified with a chemiluminescent substrate (Galactolight Plus, Tropix, Bedford, MA). Inhibitors were titrated (in duplicate) in twofold serial dilutions starting at 100 µM; percent inhibition at each concentration was calculated in relation to the control infection.

d.       Inhibition of HIV Spread

The ability of the compounds of the present invention to inhibit the spread of the human immunodeficiency virus (HIV) was measured by the method described in U.S. Patent No. 5,413,999 (May 9, 1995), and J.P. Vacca, et al., Proc.

Natl. Acad. Sci., 91: 4096-4100 (1994), which are incorporated by reference herein in their entirety.

The carbocyclic nucleoside derivatives of the present invention were  
5 also screened for cytotoxicity against cultured hepatoma (HuH-7) cells containing a  
subgenomic HCV Replicon in an MTS cell-based assay as described in the assay  
below. The HuH-7 cell line is described in H. Nakabayashi, et al., Cancer Res., 42:  
3858 (1982).

10 e. Cytotoxicity assay:

Cell cultures were prepared in appropriate media at concentrations of approximately  $1.5 \times 10^5$  cells/mL for suspension cultures in 3 day incubations and  $5.0 \times 10^4$  cells/mL for adherent cultures in 3 day incubations. 99  $\mu$ L of cell culture was transferred to wells of a 96-well tissue culture treated plate, and 1  $\mu$ L of 100-times  
15 final concentration of the test compound in DMSO was added. The plates were incubated at 37°C and 5% CO<sub>2</sub> for a specified period of time. After the incubation period, 20  $\mu$ L of CellTiter 96 Aqueous One Solution Cell Proliferation Assay reagent (MTS) (Promega) was added to each well and the plates were incubated at 37°C and 5% CO<sub>2</sub> for an additional period of time up to 3 h. The plates were agitated to mix  
20 well and absorbance at 490 nm was read using a plate reader. A standard curve of suspension culture cells was prepared with known cell numbers just prior to the addition of MTS reagent. Metabolically active cells reduce MTS to formazan. Formazan absorbs at 490 nm. The absorbance at 490 nm in the presence of compound was compared to absorbance in cells without any compound added.  
25 Reference: Cory, A. H. et al., "Use of an aqueous soluble tetrazolium/formazan assay for cell growth assays in culture," Cancer Commun. 3: 207 (1991).

The following assays were employed to measure the activity of the compounds of the present invention against other RNA-dependent RNA viruses:

30

a. Determination of In Vitro Antiviral Activity of Compounds Against Rhinovirus (Cytopathic Effect Inhibition Assay):

Assay conditions are described in the article by Sidwell and Huffman, "Use of disposable microtissue culture plates for antiviral and interferon induction studies," Appl. Microbiol. 22: 797-801 (1971).

Viruses:

Rhinovirus type 2 (RV-2), strain HGP, was used with KB cells and media (0.1% NaHCO<sub>3</sub>, no antibiotics) as stated in the Sidwell and Huffman reference. The virus,

5 obtained from the ATCC, was from a throat swab of an adult male with a mild acute febrile upper respiratory illness.

Rhinovirus type 9 (RV-9), strain 211, and rhinovirus type 14 (RV-14), strain Tow, were also obtained from the American Type Culture Collection (ATCC) in Rockville, MD. RV-9 was from human throat washings and RV-14 was from a throat swab of a 10 young adult with upper respiratory illness. Both of these viruses were used with HeLa Ohio-1 cells (Dr. Fred Hayden, Univ. of VA) which were human cervical epitheloid carcinoma cells. MEM (Eagle's minimum essential medium) with 5% Fetal Bovine serum (FBS) and 0.1% NaHCO<sub>3</sub> was used as the growth medium.

Antiviral test medium for all three virus types was MEM with 5% FBS, 0.1%

15 NaHCO<sub>3</sub>, 50 µg gentamicin/mL, and 10 mM MgCl<sub>2</sub>.

2000 µg/mL was the highest concentration used to assay the compounds of the present invention. Virus was added to the assay plate approximately 5 min after the test compound. Proper controls were also run. Assay plates were incubated with humidified air and 5% CO<sub>2</sub> at 37°C. Cytotoxicity was monitored in the control cells

20 microscopically for morphologic changes. Regression analysis of the virus CPE data and the toxicity control data gave the ED<sub>50</sub> (50% effective dose) and CC<sub>50</sub> (50% cytotoxic concentration). The selectivity index (SI) was calculated by the formula: SI = CC<sub>50</sub> ÷ ED<sub>50</sub>.

25 b. Determination of In Vitro Antiviral Activity of Compounds Against Dengue, Banzi, and Yellow Fever (CPE Inhibition Assay)

Assay details are provided in the Sidwell and Huffman reference above.

Viruses:

Dengue virus type 2, New Guinea strain, was obtained from the Center for Disease

30 Control. Two lines of African green monkey kidney cells were used to culture the virus (Vero) and to perform antiviral testing (MA-104). Both Yellow fever virus, 17D strain, prepared from infected mouse brain, and Banzi virus, H 336 strain, isolated from the serum of a febrile boy in South Africa, were obtained from ATCC. Vero cells were used with both of these viruses and for assay.

Cells and Media:

MA-104 cells (BioWhittaker, Inc., Walkersville, MD) and Vero cells (ATCC) were used in Medium 199 with 5% FBS and 0.1% NaHCO<sub>3</sub> and without antibiotics.

Assay medium for dengue, yellow fever, and Banzi viruses was MEM, 2% FBS,  
5 0.18% NaHCO<sub>3</sub> and 50 µg gentamicin/mL.

Antiviral testing of the compounds of the present invention was performed according to the Sidwell and Huffman reference and similar to the above rhinovirus antiviral testing. Adequate cytopathic effect (CPE) readings were achieved after 5-6 days for  
10 each of these viruses.

c. Determination of In Vitro Antiviral Activity of Compounds Against West Nile Virus (CPE Inhibition Assay)

Assay details are provided in the Sidwell and Huffman reference cited above. West  
15 Nile virus, New York isolate derived from crow brain, was obtained from the Center for Disease Control. Vero cells were grown and used as described above. Test medium was MEM, 1% FBS, 0.1% NaHCO<sub>3</sub> and 50 µg gentamicin/mL.

Antiviral testing of the compounds of the present invention was performed following  
20 the methods of Sidwell and Huffman which are similar to those used to assay for rhinovirus activity. Adequate cytopathic effect (CPE) readings were achieved after 5-6 days.

d. Determination of In Vitro Antiviral Activity of Compounds Against rhino, yellow fever, dengue, Banzi, and West Nile Viruses (Neutral Red Uptake Assay)

After performing the CPE inhibition assays above, an additional cytopathic detection method was used which is described in "Microtiter Assay for Interferon: Microspectrophotometric Quantitation of Cytopathic Effect," Appl. Environ. Microbiol. 31: 35-38 (1976). A Model EL309 microplate reader (Bio-Tek  
30 Instruments Inc.) was used to read the assay plate. ED<sub>50</sub>'s and CD<sub>50</sub>'s were calculated as above.

EXAMPLE OF A PHARMACEUTICAL FORMULATION

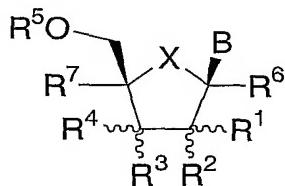
As a specific embodiment of an oral composition of a compound of the  
35 present invention, 50 mg of the compound of Example 1 or Example 2 is formulated

with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size O hard gelatin capsule.

While the invention has been described and illustrated in reference to specific embodiments thereof, those skilled in the art will appreciate that various changes, modifications, and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the preferred doses as set forth hereinabove may be applicable as a consequence of variations in the responsiveness of the human being treated for severity of the HCV infection. Likewise, the pharmacologic response observed may vary according to and depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended therefore that the invention be limited only by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

## WHAT IS CLAIMED IS:

1. A compound of structural formula I:



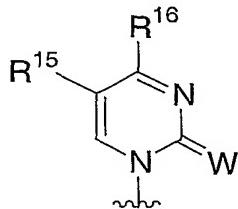
5

(I)

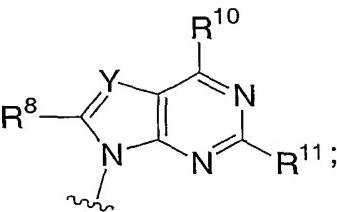
or a pharmaceutically acceptable salt thereof; wherein

n is 0, 1, or 2;

B is

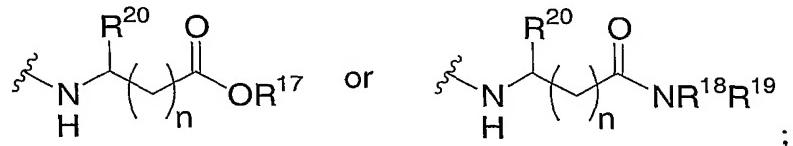


or

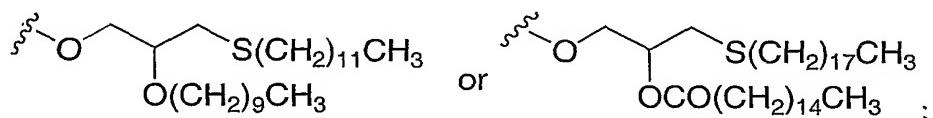


- 10 X is CH<sub>2</sub>, CHF, CF<sub>2</sub>, or C=CH<sub>2</sub>;  
 Y is N or C-R<sup>9</sup>;  
 W is O or S;  
 R<sup>1</sup> is C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, or C<sub>1-4</sub> alkyl, wherein alkyl is unsubstituted or substituted with hydroxy, amino, C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> alkylthio, or one to three fluorine atoms;  
 R<sup>2</sup> is hydrogen, fluorine, amino, hydroxy, mercapto, C<sub>1-4</sub> alkoxy, C<sub>1-8</sub> alkylcarbonyloxy, or C<sub>1-4</sub> alkyl;  
 R<sup>3</sup> and R<sup>4</sup> are each independently selected from the group consisting of hydrogen, cyano, azido, halogen, hydroxy, mercapto, amino, C<sub>1-4</sub> alkoxy, C<sub>1-8</sub> alkylcarbonyloxy, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, and C<sub>1-4</sub> alkyl, wherein alkyl is unsubstituted or substituted with hydroxy, amino, C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> alkylthio, or one to three fluorine atoms;  
 R<sup>5</sup> is hydrogen, C<sub>1-10</sub> alkylcarbonyl, P<sub>3</sub>O<sub>9</sub>H<sub>4</sub>, P<sub>2</sub>O<sub>6</sub>H<sub>3</sub>, or P(O)R<sup>13</sup>R<sup>14</sup>;

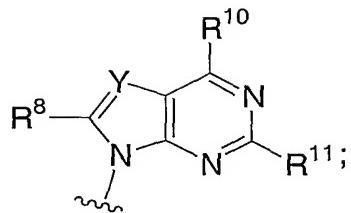
- R<sup>6</sup> and R<sup>7</sup> are each independently hydrogen, methyl, hydroxymethyl, or fluoromethyl; R<sup>8</sup> is hydrogen, C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkynyl, halogen, cyano, carboxy, C<sub>1-4</sub> alkyloxycarbonyl, azido, amino, C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub> alkyl)amino, hydroxy, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfonyl, or (C<sub>1-4</sub> alkyl)<sub>0-2</sub> aminomethyl;
- 5 R<sup>9</sup> is hydrogen, halogen, cyano, nitro, NHCONH<sub>2</sub>, CONR<sup>12</sup>R<sup>12</sup>, CSNR<sup>12</sup>R<sup>12</sup>, COOR<sup>12</sup>, C(=NH)NH<sub>2</sub>, hydroxy, C<sub>1-3</sub> alkoxy, amino, C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub> alkyl)amino, or C<sub>1-3</sub> alkyl, wherein alkyl is unsubstituted or substituted with one to three groups independently selected from halogen, amino, hydroxy, carboxy, and C<sub>1-3</sub> alkoxy;
- 10 R<sup>10</sup> and R<sup>16</sup> are each independently hydrogen, hydroxy, mercapto, halogen, C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> alkylthio, C<sub>1-8</sub> alkylcarbonyloxy, C<sub>3-6</sub> cycloalkylcarbonyloxy, C<sub>1-8</sub> alkyloxycarbonyloxy, C<sub>3-6</sub> cycloalkyloxycarbonyloxy, -OCH<sub>2</sub>CH<sub>2</sub>SC(=O)C<sub>1-4</sub> alkyl, -OCH<sub>2</sub>O(C=O)C<sub>1-4</sub> alkyl, -OCH(C<sub>1-4</sub> alkyl)O(C=O)C<sub>1-4</sub> alkyl, amino, C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub> alkyl)amino, C<sub>3-6</sub> cycloalkylamino, di(C<sub>3-6</sub> cycloalkyl)amino,
- 15 or an amino acyl residue having structural formula



- R<sup>11</sup> is hydrogen, hydroxy, halogen, C<sub>1-4</sub> alkoxy, amino, C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub> alkyl)amino, C<sub>3-6</sub> cycloalkylamino, or di(C<sub>3-6</sub> cycloalkylamino); each R<sup>12</sup> is independently hydrogen or C<sub>1-6</sub> alkyl;
- 20 R<sup>17</sup>, R<sup>18</sup>, and R<sup>19</sup> are each independently hydrogen or C<sub>1-6</sub> alkyl; R<sup>13</sup> and R<sup>14</sup> are each independently hydroxy, -OCH<sub>2</sub>CH<sub>2</sub>SC(=O)C<sub>1-4</sub> alkyl, -OCH<sub>2</sub>O(C=O)OC<sub>1-4</sub> alkyl, -NHCHMeCO<sub>2</sub>Me, -OCH(C<sub>1-4</sub> alkyl)O(C=O)C<sub>1-4</sub> alkyl,



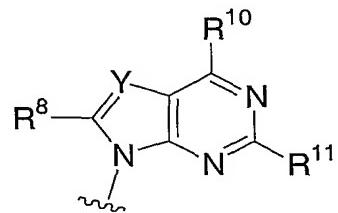
- 25 R<sup>15</sup> is hydrogen, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-4</sub> alkylamino, CF<sub>3</sub>, or halogen; and
- R<sup>20</sup> is hydrogen, C<sub>1-4</sub> alkyl, or phenyl C<sub>0-2</sub> alkyl; with the proviso that when B is



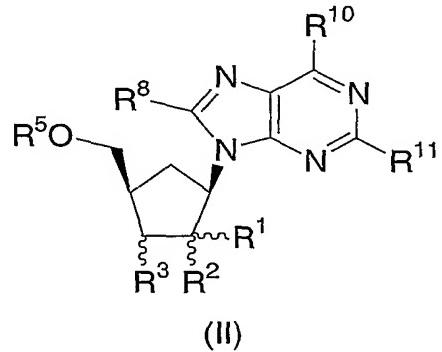
X is CH<sub>2</sub>; Y is N; R<sup>10</sup> is NH<sub>2</sub>; R<sup>2</sup> and R<sup>3</sup> are α-OH; and R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, and R<sup>11</sup> are hydrogen, then R<sup>1</sup> is not β-methyl.

5

2. The compound of Claim 1 wherein B is



3. The compound of Claim 2 of structural formula II:



10 wherein

R<sup>1</sup> is C<sub>1-3</sub> alkyl, wherein alkyl is unsubstituted or substituted with one to three fluorine atoms;

R<sup>2</sup> is hydroxy, fluoro, C<sub>1-3</sub> alkoxy, or C<sub>1-8</sub> alkylcarbonyloxy;

R<sup>3</sup> is hydrogen, halogen, hydroxy, amino, C<sub>1-3</sub> alkoxy, or C<sub>1-8</sub> alkylcarbonyloxy;

15 R<sup>5</sup> is hydrogen, C<sub>1-8</sub> alkylcarbonyl, P<sub>3</sub>O<sub>9</sub>H<sub>4</sub>, P<sub>2</sub>O<sub>6</sub>H<sub>3</sub>, or PO<sub>3</sub>H<sub>2</sub>;

R<sup>8</sup> is hydrogen, amino, or C<sub>1-4</sub> alkylamino; and

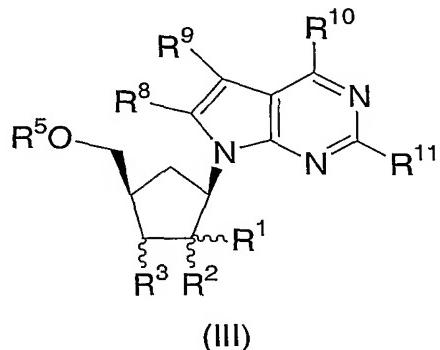
R<sup>10</sup> and R<sup>11</sup> are each independently hydrogen, halogen, hydroxy, amino, C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub> alkyl)amino, or C<sub>3-6</sub> cycloalkylamino; with the proviso that when R<sup>10</sup> is NH<sub>2</sub>, R<sup>2</sup> and R<sup>3</sup> are α-OH, and R<sup>5</sup>, R<sup>8</sup>, and R<sup>11</sup> are hydrogen, then R<sup>1</sup> is not β-methyl.

5

4. The compound of Claim 3 wherein  
 R<sup>1</sup> is methyl, fluoromethyl, difluoromethyl, or trifluoromethyl;  
 R<sup>2</sup> is hydroxy, fluoro, or methoxy;  
 R<sup>3</sup> is hydrogen, fluoro, hydroxy, amino, or methoxy;  
 10 R<sup>5</sup> is hydrogen or P<sub>3</sub>O<sub>9</sub>H<sub>4</sub>;  
 R<sup>8</sup> is hydrogen or amino; and  
 R<sup>10</sup> and R<sup>11</sup> are each independently hydrogen, fluoro, hydroxy, or amino; with the proviso that when R<sup>10</sup> is NH<sub>2</sub>, R<sup>2</sup> and R<sup>3</sup> are α-OH, and R<sup>5</sup>, R<sup>8</sup>, and R<sup>11</sup> are hydrogen, then R<sup>1</sup> is not β-methyl.

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5. The compound of Claim 2 of structural formula III:



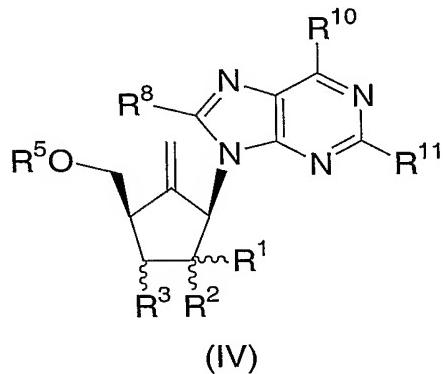
wherein

- R<sup>1</sup> is C<sub>1-3</sub> alkyl, wherein alkyl is unsubstituted or substituted with one to three  
 20 fluorine atoms;  
 R<sup>2</sup> is hydroxy, fluoro, C<sub>1-3</sub> alkoxy, or C<sub>1-8</sub> alkylcarbonyloxy;  
 R<sup>3</sup> is hydrogen, halogen, hydroxy, amino, C<sub>1-3</sub> alkoxy, or C<sub>1-8</sub> alkylcarbonyloxy;  
 R<sup>5</sup> is hydrogen, C<sub>1-8</sub> alkylcarbonyl, P<sub>3</sub>O<sub>9</sub>H<sub>4</sub>, P<sub>2</sub>O<sub>6</sub>H<sub>3</sub>, or PO<sub>3</sub>H<sub>2</sub>;  
 R<sup>8</sup> is hydrogen, amino, or C<sub>1-4</sub> alkylamino;  
 25 R<sup>9</sup> is hydrogen, cyano, methyl, halogen, CONH<sub>2</sub> or CSNH<sub>2</sub>; and  
 R<sup>10</sup> and R<sup>11</sup> are each independently hydrogen, halogen, hydroxy, amino,

C<sub>1</sub>-4 alkylamino, di(C<sub>1</sub>-4 alkyl)amino, or C<sub>3</sub>-6 cycloalkylamino.

6. The compound of Claim 5 wherein
- R<sup>1</sup> is methyl, fluoromethyl, difluoromethyl, or trifluoromethyl;
- 5 R<sup>2</sup> is hydroxy, fluoro, or methoxy;
- R<sup>3</sup> is hydrogen, fluoro, hydroxy, amino, or methoxy;
- R<sup>5</sup> is hydrogen or P<sub>3</sub>O<sub>9</sub>H<sub>4</sub>;
- R<sup>8</sup> is hydrogen or amino;
- R<sup>9</sup> is hydrogen, cyano, methyl, halogen, CONH<sub>2</sub> or CSNH<sub>2</sub>; and
- 10 R<sup>10</sup> and R<sup>11</sup> are each independently hydrogen, fluoro, hydroxy, or amino.

7. The compound of Claim 2 of structural formula IV:



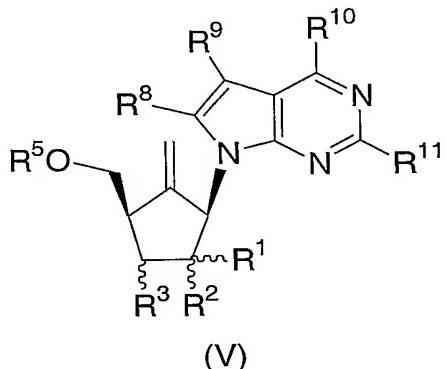
- wherein
- 15 R<sup>1</sup> is C<sub>1</sub>-3 alkyl, wherein alkyl is unsubstituted or substituted with one to three fluorine atoms;
- R<sup>2</sup> is hydroxy, fluoro, C<sub>1</sub>-3 alkoxy, or C<sub>1</sub>-8 alkylcarbonyloxy;
- R<sup>3</sup> is hydrogen, halogen, hydroxy, amino, C<sub>1</sub>-3 alkoxy, or C<sub>1</sub>-8 alkylcarbonyloxy;
- R<sup>5</sup> is hydrogen, C<sub>1</sub>-8 alkylcarbonyl, P<sub>3</sub>O<sub>9</sub>H<sub>4</sub>, P<sub>2</sub>O<sub>6</sub>H<sub>3</sub>, or PO<sub>3</sub>H<sub>2</sub>;
- 20 R<sup>8</sup> is hydrogen, amino, or C<sub>1</sub>-4 alkylamino; and
- R<sup>10</sup> and R<sup>11</sup> are each independently hydrogen, halogen, hydroxy, amino, C<sub>1</sub>-4 alkylamino, di(C<sub>1</sub>-4 alkyl)amino, or C<sub>3</sub>-6 cycloalkylamino.

8. The compound of Claim 7 wherein
- 25 R<sup>1</sup> is methyl, fluoromethyl, difluoromethyl, or trifluoromethyl;
- R<sup>2</sup> is hydroxy, fluoro, or methoxy;

R<sup>3</sup> is hydrogen, fluoro, hydroxy, amino, or methoxy;  
R<sup>5</sup> is hydrogen or P<sub>3</sub>O<sub>9</sub>H<sub>4</sub>;  
R<sup>8</sup> is hydrogen or amino; and  
R<sup>10</sup> and R<sup>11</sup> are each independently hydrogen, fluoro, hydroxy, or amino.

5

9. The compound of Claim 2 of structural formula V:



wherein

- R<sup>1</sup> is C<sub>1</sub>-3 alkyl, wherein alkyl is unsubstituted or substituted with one to three  
10 fluorine atoms;  
R<sup>2</sup> is hydroxy, fluoro, C<sub>1</sub>-3 alkoxy, or C<sub>1</sub>-8 alkylcarbonyloxy;  
R<sup>3</sup> is hydrogen, halogen, hydroxy, amino, C<sub>1</sub>-3 alkoxy, or C<sub>1</sub>-8 alkylcarbonyloxy;  
R<sup>5</sup> is hydrogen, C<sub>1</sub>-8 alkylcarbonyl, P<sub>3</sub>O<sub>9</sub>H<sub>4</sub>, P<sub>2</sub>O<sub>6</sub>H<sub>3</sub>, or PO<sub>3</sub>H<sub>2</sub>;  
R<sup>8</sup> is hydrogen, amino, or C<sub>1</sub>-4 alkylamino;  
15 R<sup>9</sup> is hydrogen, cyano, methyl, halogen, CONH<sub>2</sub> or CSNH<sub>2</sub>; and  
R<sup>10</sup> and R<sup>11</sup> are each independently hydrogen, halogen, hydroxy, amino,  
C<sub>1</sub>-4 alkylamino, di(C<sub>1</sub>-4 alkyl)amino, or C<sub>3</sub>-6 cycloalkylamino.

10. The compound of Claim 9 wherein
- 20 R<sup>1</sup> is methyl, fluoromethyl, difluoromethyl, or trifluoromethyl;  
R<sup>2</sup> is hydroxy, fluoro, or methoxy;  
R<sup>3</sup> is hydrogen, fluoro, hydroxy, amino, or methoxy;  
R<sup>5</sup> is hydrogen or P<sub>3</sub>O<sub>9</sub>H<sub>4</sub>;  
R<sup>8</sup> is hydrogen or amino;  
25 R<sup>9</sup> is hydrogen, cyano, methyl, halogen, CONH<sub>2</sub> or CSNH<sub>2</sub>; and  
R<sup>10</sup> and R<sup>11</sup> are each independently hydrogen, fluoro, hydroxy, or amino.

11. The compound of Claim 2 selected from the group consisting of:

- 5 2-amino-7-[(1 $\beta$ ,2 $\alpha$ OH,3 $\alpha$ ,4 $\beta$ )-2,3-dihydroxy-4-hydroxymethyl-2-methyl-5-methylenecyclopentyl]-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;
- 10 2-amino-7-[(1*R*,2*S*,3*R*,4*R*)-2,3-dihydroxy-4-hydroxymethyl-2-methyl-5-methylenecyclopentyl]-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;
- 15 (1 $\alpha$ OH,2 $\alpha$ ,3 $\beta$ ,5 $\beta$ )-5-(4-amino-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-3-hydroxymethyl-1-methyl-4- methylenecyclopentane-1,2-diol;
- (1*S*,2*R*,3*R*,5*R*)-5-(4-amino-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-3-hydroxymethyl-1-methyl-4- methylenecyclopentane-1,2-diol;
- 20 2-amino-9-[(1*R*,2*S*,3*R*,4*R*)-2,3-dihydroxy-4-(hydroxymethyl)-2-methyl-5-methylenecyclopentyl]-1,9-dihydro-6*H*-purin-6-one;
- 25 (1*S*,2*R*,3*R*,5*R*)-5-(6-amino-9*H*-purin-9-yl)-3-(hydroxymethyl)-1-methyl-4-methylenecyclopentane-1,2-diol;
- (1 $\alpha$ OH,2 $\alpha$ ,3 $\beta$ ,5 $\beta$ )-5-(6-amino-9*H*-purin-9-yl)-3-(hydroxymethyl)-1-methyl-4-methylenecyclopentane-1,2-diol;
- 30 (1*RS*,2*R*,3*R*,5*R*)-5-(4-amino-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-3-(hydroxymethyl)-1-methylcyclopentanediol-1,2-diol;
- (1*S*,2*R*,3*R*,5*R*)-5-(4-amino-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-3-(hydroxymethyl)-1-methylcyclopentanediol-1,2-diol;

- (1RS,2R,3R,5R)-5-(6-amino-9*H*-purin-9-yl)-3-(hydroxymethyl)-1-methylcyclopentanediol-1,2-diol;
- 5 (1S,2R,3R,5R)-5-(6-amino-9*H*-purin-9-yl)-3-(hydroxymethyl)-1-methylcyclopentanediol-1,2-diol;
- 2-amino-9-[(1R,2RS,3R,4R)-2,3-dihydroxy-4-(hydroxymethyl)-2-methylcyclopentyl]-1,9-dihydro-6*H*-purin-6-one;
- 10 2-amino-9-[(1R,2S,3R,4R)-2,3-dihydroxy-4-(hydroxymethyl)-2-methylcyclopentyl]-1,9-dihydro-6*H*-purin-6-one;
- 2-amino-7-[(1R,2RS,3R,4R)-2,3-dihydroxy-4-(hydroxymethyl)-2-methylcyclopentyl]-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one; and
- 15 2-amino-7-[(1R,2S,3R,4R)-2,3-dihydroxy-4-(hydroxymethyl)-2-methylcyclopentyl]-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;
- and the corresponding 5'-triphosphates;
- 20 or a pharmaceutically acceptable salt thereof

12. A pharmaceutical composition comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.
- 25 13. A method of treating RNA-dependent RNA virus infection comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound according to Claim 1.
- 30 14. The method of Claim 13 wherein said RNA-dependent RNA virus infection is a hepatitis C virus (HCV) infection.
15. The method of Claim 14 in combination with a therapeutically effective amount of another agent active against HCV.

16. The method of Claim 15 wherein said agent active against HCV is a 2'-C-Me-ribonucleoside; ribavirin; levovirin; thymosin alpha-1; interferon- $\beta$ ; an inhibitor of NS3 serine protease; an inhibitor of inosine monophosphate dehydrogenase; interferon- $\alpha$  or pegylated interferon- $\alpha$ , alone or in combination with 5 ribavirin or levovirin.

17. The method of Claim 16 wherein said agent active against HCV is interferon- $\alpha$  or pegylated interferon- $\alpha$ , alone or in combination with ribavirin.

10 18. Use of a compound of Claim 1 for treatment of RNA-dependent RNA virus infection in a mammal.

19. The use of Claim 18 wherein said RNA-dependent RNA virus infection is HCV infection.

15 20. Use of a compound of Claim 1 in the manufacture of a medicament for treatment of RNA-dependent RNA virus infection in a mammal.

21. The use of Claim 20 wherein said RNA-dependent RNA virus 20 infection is HCV infection.